

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Examiner: Eric E. Silverman

Syed F.A. Hossainy

Serial No. 10/815,421

Art Unit: 1615

Filed: March 31, 2004

Confirmation No. 7688

Title: BIOCOMPATIBLE POLYACRYLATE COMPOSITIONS FOR MEDICAL APPLICATIONS

Mail Stop: **Appeal Brief-Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Dear Sir:

This Appeal Brief is submitted pursuant to receipt of an Advisory Action mailed on April 14, 2008.

REAL PARTY IN INTEREST

The real party in interest with regard to this appeal is Advanced Cardiovascular Systems Inc., a California corporation, having a place of business at 3200 Lakeside Drive, Santa Clara, California 95054. The original assignment to Advanced Cardiovascular system Inc. was recorded at Reel/Frame 015510/0386 on June 28, 2004. Effective February 13, 2007, Advanced Cardiovascular Systems Inc. changed its name to Abbott Cardiovascular Systems Inc.

RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences related to or that might have any bearing, direct or indirect, on the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 1-82 are pending. Claims 1-30, 42-46, 50, and 53-82 are withdrawn.

Claims 31-41, 47-49, 51 and 52 are rejected form the subject of this appeal.

Claims 1-82 were initially filed in this case as U.S. application No. 10/815,421, filed March 31, 2004. Claims 1, 31 and 58 are independent claims. Claims 2-30 depend from claim 1, claim 32-57 depend from claim 31, and claims 59-82 depend from claim 58. A restriction requirement was mailed on July 13, 2007, restricting the claims into three groups of invention: Group I, claims 1-30, Group II, claims 31-57, and Group III, claims 58-82 (**Evidence Appendix, "A"**). The examiner also made an election of species requirement, requiring Applicant to elect a species for the genus structural component and a species for genus biobeneficial component. In response, Applicant

elected Group II inventions, claims 31-57 on August 13, 2007, for prosecution without traverse (**Evidence Appendix, "B"**). Applicant also elected poly(butyl methacrylate) (PBMA) as the species for structural component and poly(ethylene glycol)-PBMA-poly(ethylene glycol) (PEG-PBMA-PEG) as the species for biobeneficial component. An office action was mailed October 12, 2007 (**Evidence Appendix, "C"**). In the Office Action, the examiner withdrew claims 42-46 and 53-57, alleging these claims do not read upon the elected PEG-PBMA-PEG. The examiner alleged that the copending application, U.S. application No. 10/317,435, filed December 11, 2002, to which the instant application claims benefit, lacks support for PEG-PBMA-PEG and thus assigned an effective filing date of March 31, 2004 to the instant application. The examiner rejected claims 39-41 as being indefinite under 35 U.S.C. §112, 2nd paragraph for a few alleged irregularities in these claims. The examiner rejected claims 31-41, 47-49, 51 and 52 as being obvious under 35 U.S.C. §103(a) over U.S. patent No. 6,110,483 to Whitbourne et al. ("Whitbourne") (**Evidence Appendix, "D"**) in view of WO 2004/101018 ("WO 1018") (**Evidence Appendix, "E"**). The examiner stated that because Whitbourne describes PBMA and WO 1018 describes combination of PEG and PBMA, a coating as defined in claim 31 having a structural component and PEG-PBMA-PEG as a biobeneficial component would be obvious over Whitbourne and WO 1018.

In a response filed on January 9, 2008 (**Evidence Appendix, "F"**), Applicant amended the claims to overcome the rejection of claims 39-41 as being indefinite under 35 U.S.C. §112, 2nd paragraph. Applicant pointed out that PEG-PBMA-PEG is a block copolymer, which is totally different than the combination of homopolymers PEG and PBMA as described in WO 1018. Applicant further pointed out that WO 1018 and the

instant application are commonly owned and thus WO 1018 would not qualify as prior art. Applicant concluded that claims 31-41, 47-49, 51 and 52 are non-obvious.

On March 18, 2008, the examiner mailed a final office action (**Evidence Appendix, "G"**). The examiner maintained the rejection, alleging that the copolymer as defined by Applicant, which definition states that "[b]lock copolymer blocks need not be linked on the ends" (page 7, line 7 of the instant application), justifies his reading of a block copolymer as claimed to include mixtures of homopolymers (Final Office Action mailed on March 18, 2008, page 2, last paragraph). The examiner also maintained his position to include WO 1018 as prior art on the alleged basis that the instant application is entitled to March 21, 2004 as filing date but would not be able to claim the benefit of 10/317,435, filed December 11, 2002. In a response filed on April 3, 2008 (**Evidence Appendix, "H"**), Applicant pointed out that a block copolymer is a block copolymer and a person of ordinary skill in the art would recognize that a block copolymer would have a covalent chemical bond linking at least two blocks. Applicant also pointed out that a block copolymer can have blocks linked on the ends of the blocks or at least the side of one block, and thus, the definition of a block copolymer by Applicant is technically sound. Applicant further pointed out that since the cited references fail to teach PEG-PBMA-PEG, the claims are patentable over Whitbourne and WO 1018.

On April 14, 2008, an Advisory Action was mailed (**Evidence Appendix, "I"**), in which the examiner ignored Applicant's Response to Final Office and maintained the rejection of claims in the Final Office Action. The examiner indicated Amendment in the Response to Final Office Action will not be entered in the appeal.

Claims 31-41, 47-49, 51 and 52 as amended on January 9, 2008 are the subject of this appeal.

STATUS OF AMENDMENTS

The Response to Final Office Action mailed on April 3, 2008 include no amendment to claims. Amendments to the claims in the Response to Office Action filed January 9, 2008 and prior amendments have been entered and are before the Board.

SUMMARY OF THE CLAIMED SUBJECT MATTER

Claims 31-41, 47-49, 51 and 52 are drawn to a medical device.

Claim 31 is drawn to a medical device.

Claim 31 is the sole independent claim on appeal. The subject matter of claim 31 is discussed below.

Claim 31 defines a medical article comprising an implantable medical device and a coating deposited on at least a part of the device. The coating includes (a) a structural component comprising a linear acrylic homopolymer or linear acrylic copolymer; and (b) a biobeneficial component comprising a copolymer having an acrylate moiety and a biobeneficial moiety.

Support for claim 31 can be found at least at page 8, lines 4 to 9; page 8, line 15 to page 11, line 2.

The complete claim set as currently entered is provided in the **Claims Appendix**.

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

The issue presented in this appeal is:

(1) Whether claims 31-41, 47-49, 51 and 52 are obvious over Whitbourne in view of WO 1018 under 35 U.S.C. 103(a).

ARGUMENT

(1). **Claims 31-41, 47-49, 51 and 52 are non-obvious over Whitbourne in view of WO 1018 under 35 U.S.C. 103(a)**

A. The Law

Claims are non-obvious if the claimed subject matter is more than a predictable use of prior art elements according to their established functions. KSR International Co. v. Teleflex, Inc., 127 S.Ct. 1727, 1740;167 L. Ed. 2d 705, 721 ; 550 U.S. ____ ; 82 USPQ2d 1385, 1396 (2007). Although all of the elements need not be disclosed in the combination of references, “[o]ffice personnel must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art.” MPEP § 2141 (III). In addition, “[t]he gap between the prior art and the claimed invention may not be ‘so great as to render the [claim] nonobvious to one reasonably skilled in the art.’ *Id* (citing *Dann v. Johnston*, 425 U.S. 219, 230, 189 USPQ 257, 261 (1976)).” MPEP § 2141(III).

B. Analysis

a) Claimed subject matter

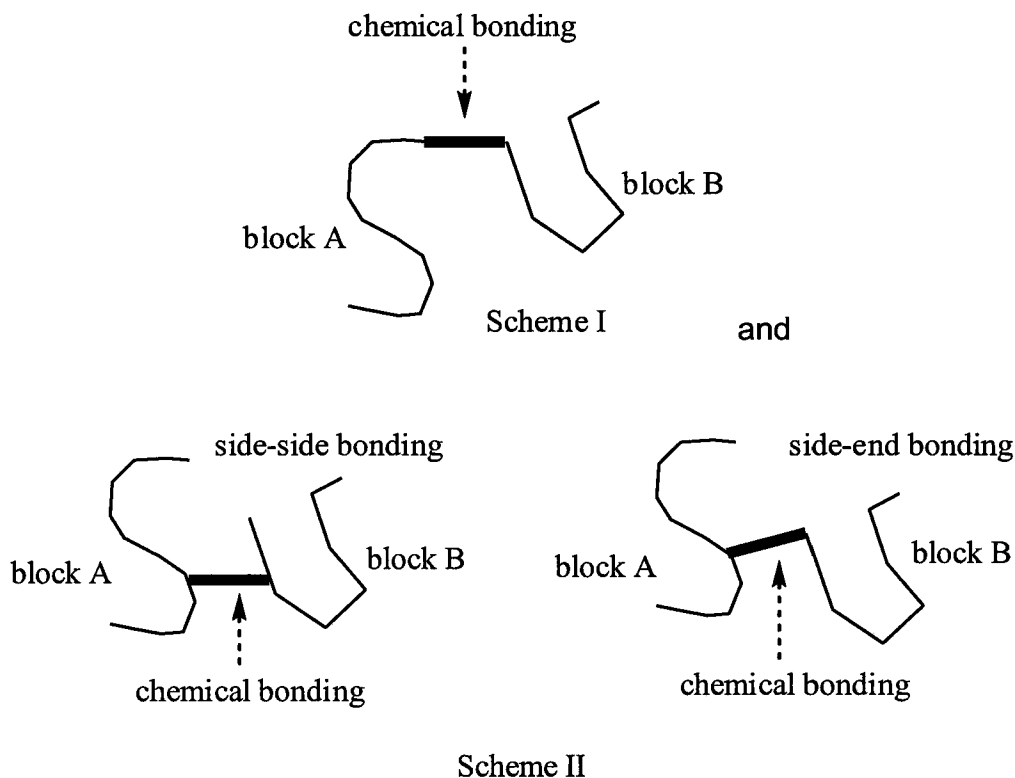
Claim 31 defines a medical article comprising an implantable medical device and a coating deposited on at least a part of the device. The coating includes (a) a structural component comprising a linear acrylic homopolymer or linear acrylic copolymer; and (b) a biobeneficial component **comprising a copolymer having an acrylate moiety and a biobeneficial moiety.**

b) Cited prior art

Whitbourne describes a coating formed of poly(butyl methacrylate) (PBMA). As the Examiner correctly notes, Whitbourne **fails to describe or teach** a coating that includes a biobeneficial component comprising a copolymer having an acrylate moiety and a biobeneficial moiety.

WO 1018 discloses a coating that can include a mixture of homopolymers PEG and PBMA. WO 1018 **does not describe or teach** a coating that includes a biobeneficial component comprising a copolymer having an acrylate moiety and a biobeneficial moiety.

However, the Examiner alleges that the definition of block copolymer by Applicant would cause a physical mixture of homopolymers of PEG and PBMA as disclosed in WO 1018 to qualify as a block copolymer because Applicant defines a block copolymer as one that “needs not be linked at ends.” This assertion is technically and legally unfounded. First, the specification of the instant application at page 4, lines 13-17 provides that the term “block copolymer” and the term “block” are used according to terminology used by the International Union of Pure and Applied Chemistry (IUPAC). Secondly, by definition, a block copolymer is a polymer that includes at least two chemically bonded blocks. For example, the chemical bonding between the two blocks can occur at the ends of the two blocks or at a position where at least one block is side-bonded to the other block, e.g., bonding via a pendant group. To be clear, the two situations are illustrated in the schemes below:



Scheme I illustrates a block copolymer having two blocks where the two blocks are chemically bonded at the ends of the two blocks. Scheme II illustrates a block copolymer having two blocks where chemical bonding between the two blocks occurs at a position where at least one block is side-bonded to the other block, e.g., bonding via a pendant group. **Applicant's definition of the block copolymer is technically sound and encompasses block copolymers as Schemes I and II illustrate.** The examiner's assertion that the block copolymer as Applicant defines encompasses a physical mixture of two homopolymers is clearly erroneous to a person of ordinary skill in the art of polymer chemistry.

In sum, WO 1018 fails to make up the deficiencies of Whitbourne with respect to the medical article as defined by claim 31. Whitbourne in view of WO 1018 would not make claim 31 *prima facie* obvious under 35 U.S.C. §103(a). Claim 31 is patentably

allowable over Whitbourne under 35 U.S.C. §103(a). Claims 32-41, 47-49, 51 and 52 depend from claim 31 and are patentably allowable over Whitbourne under 35 U.S.C. §103(a) for at least the same reason.

CONCLUSION

The examiner has failed, as a matter of law, to set forth a case of obviousness of 31-41, 47-49, 51 and 52 are obvious over Whitbourne in view of WO 1018 under 35 U.S.C. 103(a).

Appellants therefore respectfully request that the Board reverse the rejections and order the application to be passed to issue.

Date: July 30, 2008

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Respectfully submitted,

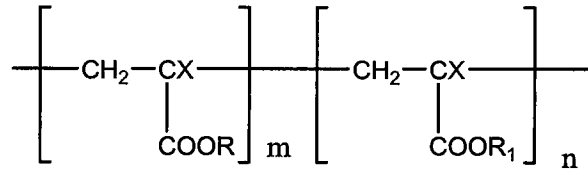
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CLAIMS APPENDIX

WHAT IS CLAIMED:

1. (Withdrawn) A composition comprising:
 - (a) a biologically compatible structural component; and
 - (b) a biobeneficial component comprising a copolymer having a biobeneficial or bioactive moiety.
2. (Withdrawn) The composition of Claim 1 wherein the biologically compatible structural component comprises a linear acrylic homopolymer or a linear acrylic copolymer.
3. (Withdrawn) The composition of Claim 1 wherein the copolymer of the biobeneficial component additional has an acrylate moiety.
4. (Withdrawn) The composition of Claim 1 coated onto an implantable medical device.
5. (Withdrawn) The composition of Claim 1 wherein the mass ratio between the structural component and the biobeneficial component is between about 99:1 and about 1:1.
6. (Withdrawn) The composition of Claim 1 wherein the mass ratio between the structural component and the biobeneficial component is between about 19:1 and about 9:1.
7. (Withdrawn) The composition of Claim 1 wherein the mass ratio between the structural component and the biobeneficial component is about 3:1.

8. (Withdrawn) The composition of Claim 2 wherein the acrylic homopolymer or linear acrylic copolymer has the structure:



wherein

- (a) X is hydrogen or methyl group;
- (b) each of R and R₁ is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl;
- (c) m is a positive integer; and
- (d) n is 0 or a positive integer.

9. (Withdrawn) The composition of Claim 2 wherein the acrylic homopolymer or linear acrylic copolymer is poly(methylmethacrylate), poly(ethylmethacrylate), poly(n-propyl methacrylate), poly(iso-propylmethacrylate), poly(n-butylmethacrylate), poly(n-laurylmethacrylate), poly(2-hydroxyethylmethacrylate), poly(methylmethacrylate-co-2-hydroxyethyl methacrylate), poly(n-butylmethacrylate-co-2-hydroxyethyl methacrylate), or mixtures thereof.

10. (Withdrawn) The composition of Claim 1 wherein the biobeneficial component includes random, block, graft or brush copolymers.

11. (Withdrawn) The composition of Claim 10 wherein the block copolymers include AB-, ABA-, BAB-, ABC-, or ABCBA-block copolymers.

12. (Withdrawn) The composition of Claim 1 wherein the biobeneficial moiety includes fragments derived from poly(alkylene glycols), superoxide dismutase-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

13. (Withdrawn) The composition of Claim 12 wherein the poly(alkylene glycols) are poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), poly(ethylene glycol-co-propylene glycol), poly(ethylene oxide-co-propylene oxide), or mixtures thereof.

14. (Withdrawn) The composition of Claim 12 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

15. (Withdrawn) The composition of Claim 12 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

16. (Withdrawn) The composition of Claim 15 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

17. (Withdrawn) The composition of Claim 16 wherein the heparin salts are sodium heparin, potassium heparin, lithium heparin, calcium heparin, magnesium heparin, adrenalin sodium, or mixtures thereof.

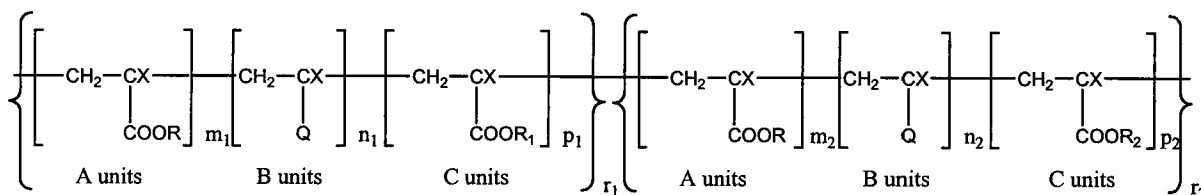
18. (Withdrawn) The composition of Claim 12 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

19. (Withdrawn) The composition of Claim 3 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 99:1 and about 1:1.

20. (Withdrawn) The composition of Claim 3 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 19:1 and about 9:1

21. (Withdrawn) The composition of Claim 3 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is about 3:1.

22. (Withdrawn) The composition of Claim 1 wherein the copolymer composing the biobeneficial component has the formula:



wherein

(a) m_1 , n_1 , p_1 , r_1 , m_2 , n_2 , p_2 , and r_2 are all integers;

(b) $m_1 \geq 0$, $n_1 > 0$, $p_1 \geq 0$, $r_1 > 0$; $m_2 \geq 0$, $n_2 > 0$, $p_2 \geq 0$, $r_2 > 0$; and

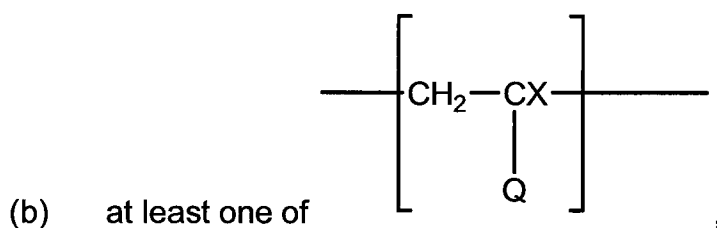
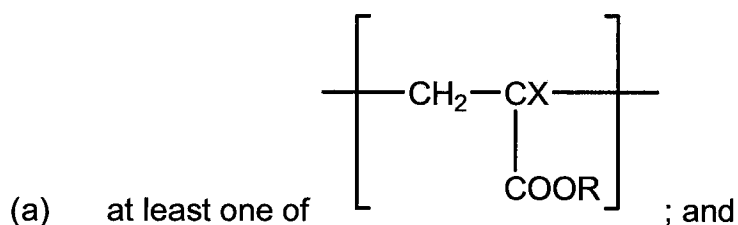
(c)

(i) if $m_1 = 0$, then $p_1 > 0$;

- (ii) if $p_1 = 0$, then $m_1 > 0$; and
 - (iii) if $m_2 = 0$, then $p_2 > 0$; and
 - (iv) if $p_2 = 0$, then $m_2 > 0$; and
 - (v) r_1 and r_2 are the same or different;
 - (vi) m_1 and m_2 are the same or different;
 - (vii) n_1 and n_2 are the same or different; and
 - (viii) p_1 and p_2 are the same or different;
- (d) X is hydrogen or methyl group;
 - (e) each of R and R_1 , independently, is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
 - (f) Q is a fragment providing the copolymer with biobeneficial or bioactive properties.

23. (Withdrawn) The composition of Claim 1 wherein the copolymer composing the biobeneficial component is poly(ethylene glycol)-block-poly(n-butylmethacrylate)-block-poly(ethylene glycol), poly(n-butylmethacrylate)-block-poly(ethylene glycol)-block-poly(n-butylmethacrylate), or mixtures thereof.

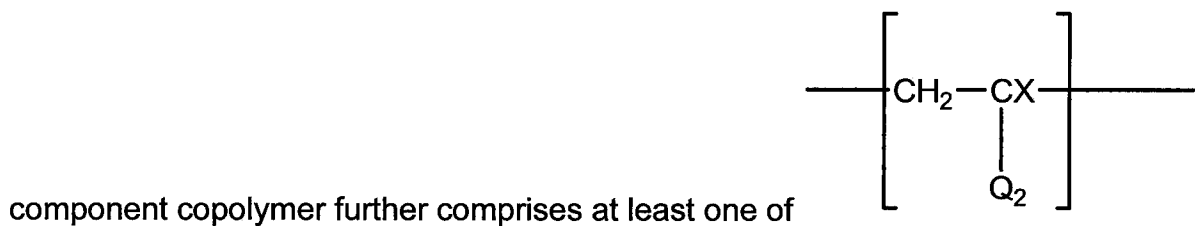
24. (Withdrawn) The composition of Claim 1 wherein the biobeneficial component includes a random, block, graft or brush copolymer comprising:



wherein

- (c) X is hydrogen or methyl group;
- (d) R is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (e) Q is a fragment providing the copolymer with biobeneficial properties.

25. (Withdrawn) The composition of Claim 24 wherein the biobeneficial



wherein Q₂ is a fragment providing the copolymer with biobeneficial or bioactive properties provided that Q₂ is different from Q.

26. (Withdrawn) The composition of Claim 24 wherein Q is derived from poly(alkylene glycols), superoxide dismutase-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

27. (Withdrawn) The composition of Claim 26 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures of these.

28. (Withdrawn) The composition of Claim 26 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or blends thereof.

29. (Withdrawn) The composition of Claim 26 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

30. (Withdrawn) The composition of Claim 26 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

31. (Original) A medical article comprising an implantable medical device and a coating deposited on at least a part of the device, the coating including:

- (a) a structural component comprising a linear acrylic homopolymer or linear acrylic copolymer; and
- (b) a biobeneficial component comprising a copolymer having an acrylate moiety and a biobeneficial moiety.

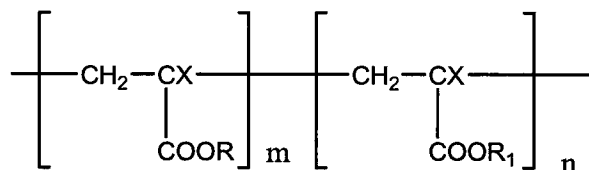
32. (Original) The medical article of Claim 31 wherein the implantable medical device is a stent.

33. (Original) The medical article of Claim 31 wherein the mass ratio between the structural component and the biobeneficial component is between about 99:1 and about 1:1.

34. (Original) The medical article of Claim 31 wherein the mass ratio between the structural component and the biobeneficial component is between about 19:1 and about 9:1.

35. (Original) The medical article of Claim 31 wherein the mass ratio between the structural component and the biobeneficial component is about 3:1.

36. (Original) The medical article of Claim 31 wherein the acrylic homopolymer and linear acrylic copolymer have the structure:



wherein

- (a) X is hydrogen or methyl group;
- (b) each of R and R₁ is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl;
- (c) m is a positive integer; and

(d) n is 0 or a positive integer.

37. (Original) The medical article of Claim 31 wherein the acrylic homopolymer or linear acrylic copolymer are poly(methylmethacrylate), poly(ethylmethacrylate), poly(n-propyl methacrylate), poly(iso-propylmethacrylate), poly(n-butylmethacrylate), poly(n-laurylmethacrylate), poly(2-hydroxyethylmethacrylate), poly(methylmethacrylate-co-2-hydroxyethyl methacrylate), poly(n-butylmethacrylate-co-2-hydroxyethyl methacrylate), or mixtures thereof.

38. (Original) The medical article of Claim 31 wherein the biobeneficial component includes random, block, graft or brush copolymers.

39. (Previously presented) The medical article of Claim 38 wherein the block copolymers include AB, ABA, BAB, ABC, or ABCBA block copolymers.

40. (Previously presented) The medical article of Claim 31 wherein the biobeneficial moiety is from poly(alkylene glycols), superoxide dismutase-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

41. (Original) The medical article of Claim 40 wherein the poly(alkylene glycols) are poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), poly(ethylene glycol-co-propylene glycol), poly(ethylene oxide-co-propylene oxide), or mixtures thereof.

42. (Withdrawn) The medical article of Claim 40 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

43. (Withdrawn) The medical article of Claim 40 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

44. (Withdrawn) The medical article of Claim 43 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

45. (Withdrawn) The medical article of Claim 44 wherein the heparin salts are sodium heparin, potassium heparin, lithium heparin, calcium heparin, magnesium heparin, ardeparin sodium, or mixtures thereof.

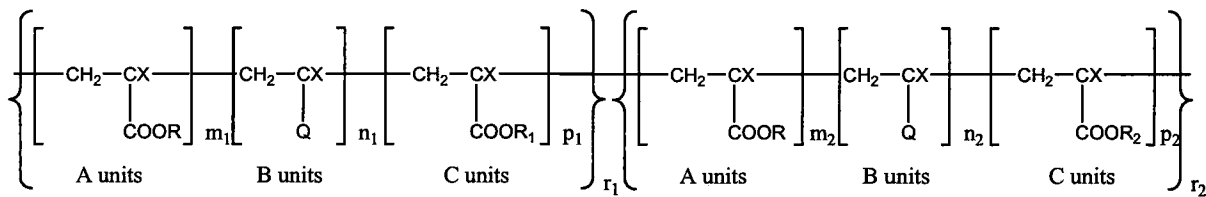
46. (Withdrawn) The medical article of Claim 40 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

47. (Original) The medical article of Claim 31 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 99:1 and about 1:1.

48. (Original) The medical article of Claim 31 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 19:1 and about 9:1

49. (Original) The medical article of Claim 31 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is about 3:1.

50. (Withdrawn) The medical article of Claim 31 wherein the copolymer composing the biobeneficial component has the formula:



wherein

(a) m_1 , n_1 , p_1 , r_1 , m_2 , n_2 , p_2 , and r_2 are all integers;

(b) $m_1 \geq 0$, $n_1 > 0$, $p_1 \geq 0$, $r_1 > 0$; $m_2 \geq 0$, $n_2 > 0$, $p_2 \geq 0$, $r_2 > 0$; and

(c)

(i) if $m_1 = 0$, then $p_1 > 0$;

(ii) if $p_1 = 0$, then $m_1 > 0$; and

(iii) if $m_2 = 0$, then $p_2 > 0$; and

(iv) if $p_2 = 0$, then $m_2 > 0$; and

(v) r_1 and r_2 are the same or different;

(vi) m_1 and m_2 are the same or different;

(vii) n_1 and n_2 are the same or different; and

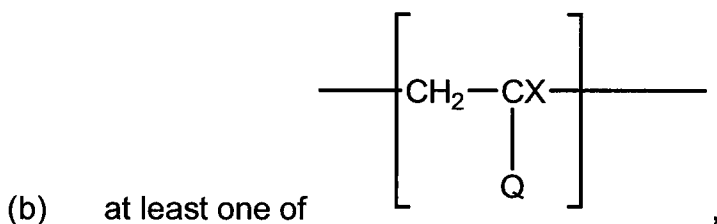
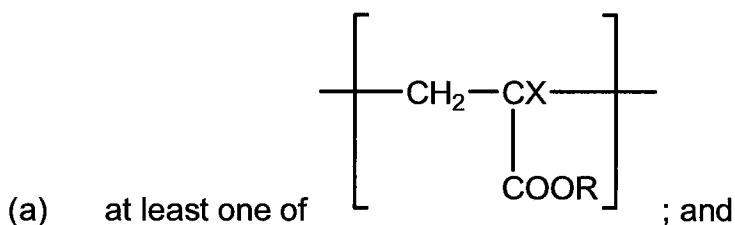
(viii) p_1 and p_2 are the same or different;

(d) X is hydrogen or methyl group;

- (e) each of R and R₁, independently, is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (f) Q is a fragment providing the copolymer with biobeneficial properties.

51. (Original) The medical article of Claim 31 wherein the copolymer composing the biobeneficial component is poly(ethylene glycol)-block-poly(n-butylmethacrylate)-block-poly(ethylene glycol), or poly(n-butylmethacrylate)-block-poly(ethylene glycol)-block-poly(n-butylmethacrylate).

52. (Original) The medical article of Claim 31 wherein the biobeneficial component includes a random, block, graft or brush copolymer composed of:



wherein

- (c) X is hydrogen or methyl group;
- (d) R is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and

- (e) Q is a fragment providing the copolymer with biobeneficial properties.

53. (Original) The composition of Claim 52 wherein Q is derived from poly(alkylene glycols), superoxide dismutate-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

54. (Original) The composition of Claim 53 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

55. (Original) The composition of Claim 53 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

56. (Original) The composition of Claim 53 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

57. (Original) The composition of Claim 53 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

58. (Withdrawn) A method for fabricating a medical article comprising depositing a polymeric blend comprising:

- (a) a biologically compatible structural component; and

- (b) a biobeneficial component comprising a copolymer having a biobeneficial or bioactive moiety.

on at least a portion of the implantable medical device to form a coating.

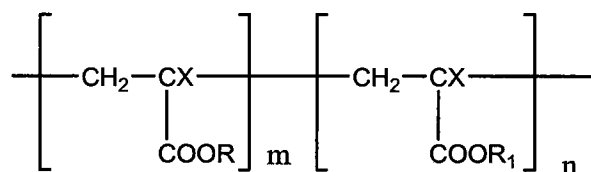
59. (Withdrawn) The method of Claim 58 wherein the implantable medical device is a stent.

60. (Withdrawn) The method of Claim 58 wherein the mass ratio between the structural component and the biobeneficial component is between about 99:1 and about 1:1.

61. (Withdrawn) The method of Claim 58 wherein the mass ratio between the structural component and the biobeneficial component is between about 19:1 and about 9:1.

62. (Withdrawn) The method of Claim 58 wherein the mass ratio between the structural component and the biobeneficial component is about 3:1.

63. (Withdrawn) The method of Claim 58 wherein the acrylic homopolymer or linear acrylic copolymer have the structure:



wherein

- (a) X is hydrogen or methyl group;

- (b) each of R and R₁ is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl;
- (c) m is a positive integer; and
- (d) n is 0 or a positive integer.

64. (Withdrawn) The method of Claim 58 wherein the acrylic homopolymer and linear acrylic copolymer are synthesized by polymerizing monomers selected from a group consisting of methylmethacrylate, ethylmethacrylate, n-propyl methacrylate, isopropylmethacrylate, n-butylmethacrylate, n-laurylmethacrylate, 2-hydroxyethylmethacrylate, and mixtures thereof.

65. (Withdrawn) The method of Claim 58 wherein the step of preparing the polymeric blend includes synthesizing the biobeneficial random, block, graft or brush copolymers.

66. (Withdrawn) The method of Claim 65 wherein the block copolymers include AB-, ABA-, BAB-, ABC-, or ABCBA-block copolymers.

67. (Withdrawn) The method of Claim 65 wherein the step of synthesizing the block copolymers includes copolymerizing an acrylate and a biobeneficial monomer by a method of living, free-radical copolymerization with initiation-transfer agent termination of the living macro chains.

68. (Withdrawn) The method of Claim 67 wherein the acrylate is methylmethacrylate, ethylmethacrylate, n-propyl methacrylate, isopropylmethacrylate, n-butylmethacrylate, n-laurylmethacrylate, 2-hydroxyethylmethacrylate, or mixtures thereof.

69. (Withdrawn) The method of Claim 67 wherein the biobeneficial monomer includes acryloyl-, methacryloyl-, vinyl, or allyl-modified adducts of superoxide dismutase-mimetics; acryloyl-, methacryloyl-, vinyl, or allyl-modified diazenium diolate type nitric oxide donors; or acryloyl-, methacryloyl-, vinyl, or allyl-modified polycationic peptides.

70. (Withdrawn) The method of Claim 67 wherein the biobeneficial monomer is 2-acrylamido-2-methyl-1-propanesulfonic acid, poly(ethylene glycol) methacrylate, 3-sulfopropyl acrylate, 3-sulfopropyl acrylate methacrylate, N-vinylpyrrolidone, vinyl sulfonic acid, 4-styrene sulfonic acid, or 3-allyloxy-2-hydroxypropanesulfonic acid.

71. (Withdrawn) The method of Claim 58 wherein the biobeneficial moiety includes fragments derived from poly(alkylene glycols), superoxide dismutase-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

72. (Withdrawn) The method of Claim 71 wherein the poly(alkylene glycols) are poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), poly(ethylene glycol-co-propylene glycol), poly(ethylene oxide-co-propylene oxide), or mixtures thereof.

73. (Withdrawn) The method of Claim 71 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

74. (Withdrawn) The method of Claim 71 wherein the polysaccharides are heparin, heparin derivatives, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

75. (Withdrawn) The method of Claim 74 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

76. (Withdrawn) The method of Claim 75 wherein the heparin salts are sodium heparin, potassium heparin, lithium heparin, calcium heparin, magnesium heparin, ardeparin sodium, or mixtures thereof.

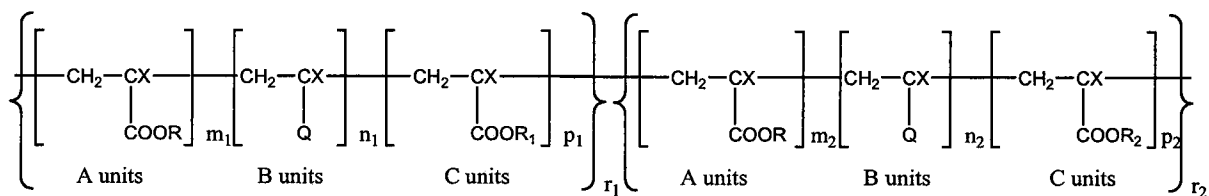
77. (Withdrawn) The method of Claim 71 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropane sulfonic acid, or mixtures thereof.

78. (Withdrawn) The method of Claim 58 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 99:1 and about 1:1.

79. (Withdrawn) The method of Claim 58 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 19:1 and about 9:1

80. (Withdrawn) The method of Claim 58 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is about 3:1.

81. (Withdrawn) The method of Claim 58 wherein the copolymer comprising the biobeneficial component has the formula:



wherein

- (a) $m_1, n_1, p_1, r_1, m_2, n_2, p_2,$ and r_2 are all integers;
- (b) $m_1 \geq 0, n_1 > 0, p_1 \geq 0, r_1 > 0; m_2 \geq 0, n_2 > 0, p_2 \geq 0, r_2 > 0;$ and
- (c)
 - (i) if $m_1 = 0$, then $p_1 > 0$;
 - (ii) if $p_1 = 0$, then $m_1 > 0$; and
 - (iii) if $m_2 = 0$, then $p_2 > 0$; and
 - (iv) if $p_2 = 0$, then $m_2 > 0$; and
 - (v) r_1 and r_2 are the same or different;
 - (vi) m_1 and m_2 are the same or different;
 - (vii) n_1 and n_2 are the same or different; and
 - (viii) p_1 and p_2 are the same or different;
- (d) X is hydrogen or methyl group;
- (e) each of R and R_1 , independently, is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (f) Q is a fragment providing the copolymer with biobeneficial properties.

82. (Withdrawn) The method of Claim 58 wherein the copolymer comprising the biobeneficial component is poly(ethylene glycol)-block-poly(n-butylmethacrylate)-block-poly(ethylene glycol), poly(n-butylmethacrylate)-block-poly(ethylene glycol)-block-poly(n-butylmethacrylate), or mixtures thereof.

EVIDENCE APPENDIX

Attached hereto are the following:

- (A) Restriction Requirement mailed July 13, 2007;
- (B) Response to Restriction Requirement filed on August 13, 2007;
- (C) Office Action mailed October 12, 2007;
- (D) U.S. patent No. 6,110,483 to Whitbourne et al. ("Whitbourne");
- (E) WO 2004/101018 ("WO 1018");
- (F) Response to Office Action filed January 9, 2008;
- (G) Final Office Action mailed March 18, 2008;
- (H) Response to Final Office Action filed April 3, 2008; and
- (I) Advisory Action mailed on April 14, 2008.

RELATED PROCEEDINGS APPENDIX

There are no related proceedings.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,421	03/31/2004	Syed F.A. Hossainy	50623.359	7688

7590
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Squire, Sanders & Dempsey L.L.P.
Suite 300
1 Maritime Plaza
San Francisco, CA 94111

07/13/2007

DOCKETED:

RESTRICTION: 8/12/07

JUL 18 2007

BY: tlb Atty: CK
SQUIRE, SANDERS & DEMPSEY

EXAMINER

SILVERMAN, ERIC E

ART UNIT PAPER NUMBER

1615

MAIL DATE DELIVERY MODE

07/13/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/815,421	HOSSAINY, SYED F.A.	
	Examiner	Art Unit	
	Eric E. Silverman, PhD	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION. 7/18/07: confirmed it should be 1 mo/30 days w/ ex. silverman

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-82 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) ____ is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☒ Claim(s) 1-82 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1 – 30, drawn to a polymer-based composition, classified in class 514, subclass 772.1.
- II. Claims 31 - 57, drawn to an implantable medical device, classified in class 424, subclass 422.
- III. Claims 58 - 82, drawn to a method of making a medical article, classified in class 424 subclass 400

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as mutually exclusive species in an intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product, and the species are patentably distinct (MPEP § 806.05(j)). In the instant case, the intermediate product is deemed to be useful as a matrix drug delivery form, or a wound healing composition, or a commodity plastic and the inventions are deemed patentably distinct because there is nothing on this record to show them to be obvious variants.

Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the product

of Group I can be used in a materially different process, such as a process of making a commodity plastic.

Inventions II and III are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the product of Group II can be made by a materially different process, such as by depositing layers a biologically compatible structural component and a biobeneficial component without blending the two (for example, by layer-by-layer deposition of the two components).

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification, restriction for examination purposes as indicated is proper.

This application contains claims directed to the following patentably distinct species: **1)** different species of biologically compatible structural components (component (a) in claims 1, 31 and 58), and **2)** the biobeneficial component comprising a copolymer having a biobeneficial or bioactive moiety (component (b) in claims 1, 31, and 58). The species are independent or distinct because each species of different material has a different chemical structure, and thus has different physical, chemical, and biological properties associated with the particular structure of each species.

Applicants' response to the election of **1**, the species of biologically compatible structural component, will include the election of the polymer which makes up this component. The election will specify each and every monomer in the polymer by name

Art Unit: 1615

or chemical structure (for example, methyl methacrylate, acrylic acid, acrylamide, etc), and if the elected species is a copolymer, will further specify the disposition of each and every comonomer with respect to the other comonomers (for example, an A-B copolymer wherein A is methyl methacrylate and B is n-butyl acrylate, which would read on claim 8).

Applicants' response to the election of **2**, the species of biobeneficial component comprising copolymer having a biobeneficial or bioactive moiety will specify the chemical structure of this component. The response will specify, for example, one of the specific poly(alkylene glycols) of claim 13 (such as poly(ethylene glycol) or poly(ethylene oxide-co-polypropylene oxide)) or one other **specific** biobeneficial component claimed. The election will specify each and every element of the biobeneficial component.

The election of species outlined above is required regardless of which Group is elected. A fully responsive requirement will include the election a Group, a species **1** and a species **2**.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1, 31, and 58 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after

Art Unit: 1615

the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Because this requirement is complex, a telephonic election was not solicited.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

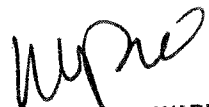
Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

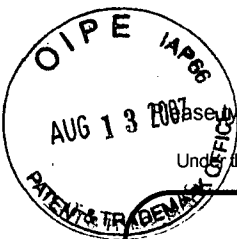
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric E. Silverman, PhD whose telephone number is 571 272 5549. The examiner can normally be reached on Monday to Friday 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571 272 8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric E. Silverman, PhD
Art Unit 1615


MICHAEL P. WOODWARD
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600



08-15-07

1FW

PTO/SB/21 (08-03)

Please type a plus sign (+) inside this box → ☒

Approved for use through 10/31/2006. OMB 0651-0031

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**TRANSMITTAL
FORM**

(to be used for all correspondence after initial filing)

Application Number	10/815,421
Filing Date	March 31, 2004
First Named Inventor	Syed F.A. Hossainy
Group Art Unit	1615
Examiner Name	Eric E. Silverman
Attorney Docket Number	50623.359

Total Number of Pages in This Submission
(excluding references)

22

ENCLOSURES (check all that apply)

<input checked="" type="checkbox"/> Deposit Account 07-1850 Authorization	<input type="checkbox"/> Assignment Papers (for an Application)	<input type="checkbox"/> After Allowance Communication to Group
<input checked="" type="checkbox"/> Postage Paid Return Postcard	<input checked="" type="checkbox"/> Response to Election Of Species Requirement (21 pages)	<input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences
<input type="checkbox"/> Amendment / Response	<input type="checkbox"/> Issue Fee Transmittal with PTO-85b (in duplicate)	<input type="checkbox"/> Appeal Communication to Group (Appeal Notice, Brief, Reply Brief)
<input type="checkbox"/> Amendment Transmittal Letter (in duplicate)	<input type="checkbox"/> Petition	<input type="checkbox"/> Proprietary Information
<input type="checkbox"/> Affidavits/declaration(s)	<input type="checkbox"/> Petition to Convert to a Provisional Application	<input type="checkbox"/> Status Letter
<input type="checkbox"/> Petition for Extension of Time (___ months) (in duplicate)	<input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address	<input type="checkbox"/> Other Enclosure(s) (please identify below):
<input type="checkbox"/> Information Disclosure Statement (in duplicate) with Form PTO-1449 and References	<input type="checkbox"/> Terminal Disclaimer	
<input checked="" type="checkbox"/> Express Mail Label No. EV 889007300 US	<input type="checkbox"/> Request for Refund	
<input checked="" type="checkbox"/> Certificate of Mailing	<input type="checkbox"/> CD, Number of CD(s) _____	
<input type="checkbox"/> Response to Missing Parts/ Incomplete Application	Remarks	
<input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Squire, Sanders & Dempsey L.L.P. Zhaoyang Li, Ph.D., Reg. No. 46,872
Signature	
Date	August 13, 2007

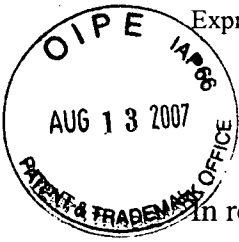
CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date below:

Typed or printed name	Rebecca M. Klits		
Signature		Date	August 13, 2007

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Examiner: Eric E. Silverman

Syed Faiyaz Ahmed Hossainy

Serial No. 10/815,421

Art Unit: 1615

Filed: March 31, 2004

Title: BIOCOMPATIBLE POLYACRYLATE COMPOSITIONS FOR MEDICAL APPLICATIONS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

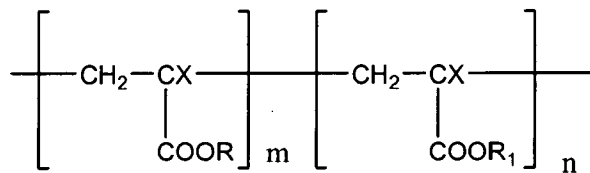
Response to Restriction Requirement

Dear Examiner Silverman:

This response addresses the Restriction Requirement mailed on July 13, 2007.

In the Claims

1. (Withdrawn) A composition comprising:
 - (a) a biologically compatible structural component; and
 - (b) a biobeneficial component comprising a copolymer having a biobeneficial or bioactive moiety.
2. (Withdrawn) The composition of Claim 1 wherein the biologically compatible structural component comprises a linear acrylic homopolymer or a linear acrylic copolymer.
3. (Withdrawn) The composition of Claim 1 wherein the copolymer of the biobeneficial component additional has an acrylate moiety.
4. (Withdrawn) The composition of Claim 1 coated onto an implantable medical device.
5. (Withdrawn) The composition of Claim 1 wherein the mass ratio between the structural component and the biobeneficial component is between about 99:1 and about 1:1.
6. (Withdrawn) The composition of Claim 1 wherein the mass ratio between the structural component and the biobeneficial component is between about 19:1 and about 9:1.
7. (Withdrawn) The composition of Claim 1 wherein the mass ratio between the structural component and the biobeneficial component is about 3:1.
8. (Withdrawn) The composition of Claim 2 wherein the acrylic homopolymer or linear acrylic copolymer has the structure:



wherein

- (a) X is hydrogen or methyl group;
- (b) each of R and R₁ is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl;
- (c) m is a positive integer; and
- (d) n is 0 or a positive integer.

9. (Withdrawn) The composition of Claim 2 wherein the acrylic homopolymer or linear acrylic copolymer is poly(methylmethacrylate), poly(ethylmethacrylate), poly(n-propyl methacrylate), poly(iso-propylmethacrylate), poly(n-butylmethacrylate), poly(n-laurylmethacrylate), poly(2-hydroxyethylmethacrylate), poly(methylmethacrylate-co-2-hydroxyethyl methacrylate), poly(n-butylmethacrylate-co-2-hydroxyethyl methacrylate), or mixtures thereof.

10. (Withdrawn) The composition of Claim 1 wherein the biobeneficial component includes random, block, graft or brush copolymers.

11. (Withdrawn) The composition of Claim 10 wherein the block copolymers include AB-, ABA-, BAB-, ABC-, or ABCBA-block copolymers.

12. (Withdrawn) The composition of Claim 1 wherein the biobeneficial moiety includes fragments derived from poly(alkylene glycols), superoxide dismutase-mimetics (SODm),

diazonium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

13. (Withdrawn) The composition of Claim 12 wherein the poly(alkylene glycols) are poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), poly(ethylene glycol-co-propylene glycol), poly(ethylene oxide-co-propylene oxide), or mixtures thereof.

14. (Withdrawn) The composition of Claim 12 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

15. (Withdrawn) The composition of Claim 12 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

16. (Withdrawn) The composition of Claim 15 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

17. (Withdrawn) The composition of Claim 16 wherein the heparin salts are sodium heparin, potassium heparin, lithium heparin, calcium heparin, magnesium heparin, adrenalin sodium, or mixtures thereof.

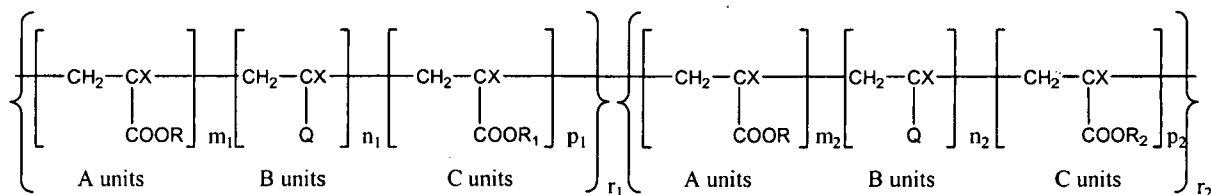
18. (Withdrawn) The composition of Claim 12 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

19. (Withdrawn) The composition of Claim 3 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 99:1 and about 1:1.

20. (Withdrawn) The composition of Claim 3 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 19:1 and about 9:1

21. (Withdrawn) The composition of Claim 3 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is about 3:1.

22. (Withdrawn) The composition of Claim 1 wherein the copolymer composing the biobeneficial component has the formula:



wherein

(a) $m_1, n_1, p_1, r_1, m_2, n_2, p_2,$ and r_2 are all integers;

(b) $m_1 \geq 0, n_1 > 0, p_1 \geq 0, r_1 > 0; m_2 \geq 0, n_2 > 0, p_2 \geq 0, r_2 > 0;$ and

(c)

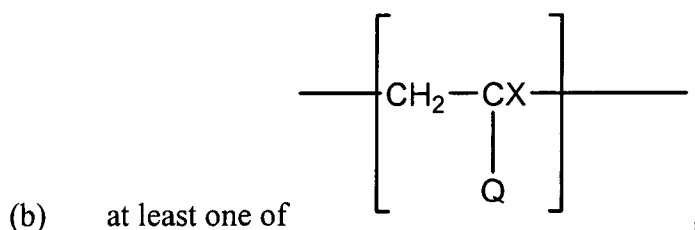
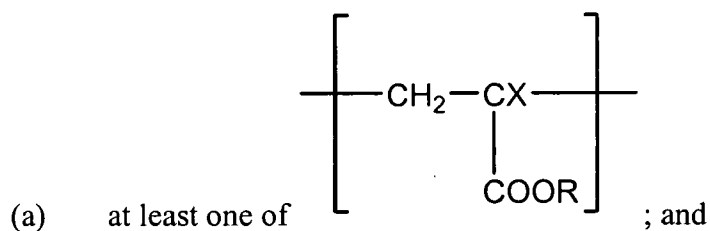
(i) if $m_1 = 0$, then $p_1 > 0$;

(ii) if $p_1 = 0$, then $m_1 > 0$; and

- (iii) if $m_2 = 0$, then $p_2 > 0$; and
 - (iv) if $p_2 = 0$, then $m_2 > 0$; and
 - (v) r_1 and r_2 are the same or different;
 - (vi) m_1 and m_2 are the same or different;
 - (vii) n_1 and n_2 are the same or different; and
 - (viii) p_1 and p_2 are the same or different;
- (d) X is hydrogen or methyl group;
- (e) each of R and R_1 , independently, is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (f) Q is a fragment providing the copolymer with biobeneficial or bioactive properties.

23. (Withdrawn) The composition of Claim 1 wherein the copolymer composing the biobeneficial component is poly(ethylene glycol)-block-poly(n-butylmethacrylate)-block-poly(ethylene glycol), poly(n-butylmethacrylate)-block-poly(ethylene glycol)-block-poly(n-butylmethacrylate), or mixtures thereof.

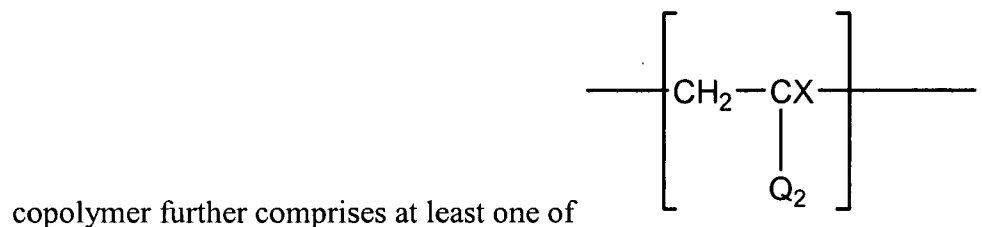
24. (Withdrawn) The composition of Claim 1 wherein the biobeneficial component includes a random, block, graft or brush copolymer comprising:



wherein

- (c) X is hydrogen or methyl group;
- (d) R is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (e) Q is a fragment providing the copolymer with biobeneficial properties.

25. (Withdrawn) The composition of Claim 24 wherein the biobeneficial component



wherein Q₂ is a fragment providing the copolymer with biobeneficial or bioactive properties provided that Q₂ is different from Q.

26. (Withdrawn) The composition of Claim 24 wherein Q is derived from poly(alkylene glycols), superoxide dismutase-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

27. (Withdrawn) The composition of Claim 26 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures of these.

28. (Withdrawn) The composition of Claim 26 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or blends thereof.

29. (Withdrawn) The composition of Claim 26 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

30. (Withdrawn) The composition of Claim 26 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

31. (Original) A medical article comprising an implantable medical device and a coating deposited on at least a part of the device, the coating including:

- (a) a structural component comprising a linear acrylic homopolymer or linear acrylic copolymer; and

- (b) a biobeneficial component comprising a copolymer having an acrylate moiety and a biobeneficial moiety.

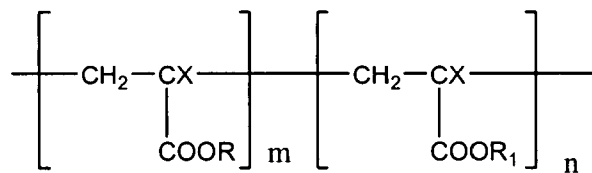
32. (Original) The medical article of Claim 31 wherein the implantable medical device is a stent.

33. (Original) The medical article of Claim 31 wherein the mass ratio between the structural component and the biobeneficial component is between about 99:1 and about 1:1.

34. (Original) The medical article of Claim 31 wherein the mass ratio between the structural component and the biobeneficial component is between about 19:1 and about 9:1.

35. (Original) The medical article of Claim 31 wherein the mass ratio between the structural component and the biobeneficial component is about 3:1.

36. (Original) The medical article of Claim 31 wherein the acrylic homopolymer and linear acrylic copolymer have the structure:



wherein

- (a) X is hydrogen or methyl group;
- (b) each of R and R₁ is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl;
- (c) m is a positive integer; and

(d) n is 0 or a positive integer.

37. (Original) The medical article of Claim 31 wherein the acrylic homopolymer or linear acrylic copolymer are poly(methylmethacrylate), poly(ethylmethacrylate), poly(n-propyl methacrylate), poly(iso-propylmethacrylate), poly(n-butylmethacrylate), poly(n-laurylmethacrylate), poly(2-hydroxyethylmethacrylate), poly(methylmethacrylate-co-2-hydroxyethyl methacrylate), poly(n-butylmethacrylate-co-2-hydroxyethyl methacrylate), or mixtures thereof.

38. (Original) The medical article of Claim 31 wherein the biobeneficial component includes random, block, graft or brush copolymers.

39. (Original) The medical article of Claim 38 wherein the block copolymers include AB-, ABA-, BAB-, ABC-, or ABCBA-block copolymers.

40. (Original) The medical article of Claim 31 wherein the biobeneficial moiety includes fragments derived from poly(alkylene glycols), superoxide dismutase-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

41. (Original) The medical article of Claim 40 wherein the poly(alkylene glycols) are poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), poly(ethylene glycol-co-propylene glycol), poly(ethylene oxide-co-propylene oxide), or mixtures thereof.

42. (Original) The medical article of Claim 40 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

43. (Original) The medical article of Claim 40 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

44. (Original) The medical article of Claim 43 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

45. (Original) The medical article of Claim 44 wherein the heparin salts are sodium heparin, potassium heparin, lithium heparin, calcium heparin, magnesium heparin, ardeparin sodium, or mixtures thereof.

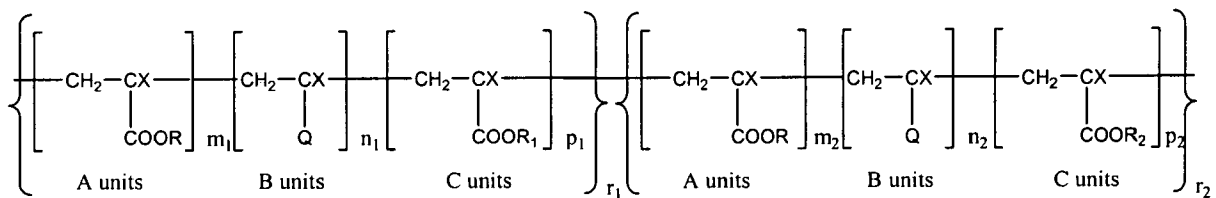
46. (Original) The medical article of Claim 40 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

47. (Original) The medical article of Claim 31 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 99:1 and about 1:1.

48. (Original) The medical article of Claim 31 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 19:1 and about 9:1

49. (Original) The medical article of Claim 31 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is about 3:1.

50. (Original) The medical article of Claim 31 wherein the copolymer composing the biobeneficial component has the formula:



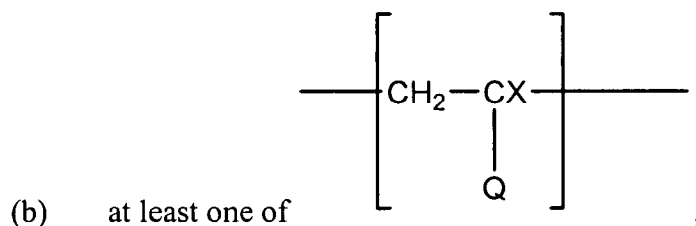
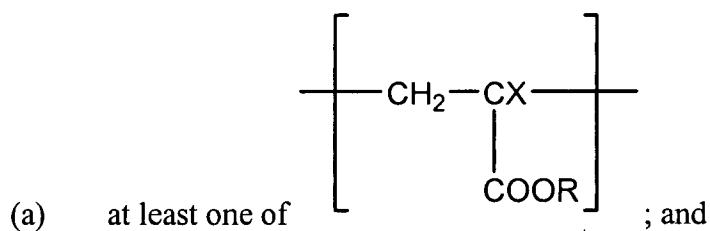
wherein

- (a) $m_1, n_1, p_1, r_1, m_2, n_2, p_2,$ and r_2 are all integers;
- (b) $m_1 \geq 0, n_1 > 0, p_1 \geq 0, r_1 > 0; m_2 \geq 0, n_2 > 0, p_2 \geq 0, r_2 > 0;$ and
- (c)
 - (i) if $m_1 = 0$, then $p_1 > 0$;
 - (ii) if $p_1 = 0$, then $m_1 > 0$; and
 - (iii) if $m_2 = 0$, then $p_2 > 0$; and
 - (iv) if $p_2 = 0$, then $m_2 > 0$; and
 - (v) r_1 and r_2 are the same or different;
 - (vi) m_1 and m_2 are the same or different;
 - (vii) n_1 and n_2 are the same or different; and
 - (viii) p_1 and p_2 are the same or different;

- (d) X is hydrogen or methyl group;
- (e) each of R and R₁, independently, is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (f) Q is a fragment providing the copolymer with biobeneficial properties.

51. (Original) The medical article of Claim 31 wherein the copolymer composing the biobeneficial component is poly(ethylene glycol)-block-poly(n-butylmethacrylate)-block-poly(ethylene glycol), or poly(n-butylmethacrylate)-block-poly(ethylene glycol)-block-poly(n-butylmethacrylate).

52. (Original) The medical article of Claim 31 wherein the biobeneficial component includes a random, block, graft or brush copolymer composed of:



wherein

- (c) X is hydrogen or methyl group;

- (d) R is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (e) Q is a fragment providing the copolymer with biobeneficial properties.

53. (Original) The composition of Claim 52 wherein Q is derived from poly(alkylene glycols), superoxide dismutase-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

54. (Original) The composition of Claim 53 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

55. (Original) The composition of Claim 53 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

56. (Original) The composition of Claim 53 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

57. (Original) The composition of Claim 53 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

58. (Withdrawn) A method for fabricating a medical article comprising depositing a polymeric blend comprising:

- (a) a biologically compatible structural component; and
- (b) a biobeneficial component comprising a copolymer having a biobeneficial or bioactive moiety.

on at least a portion of the implantable medical device to form a coating.

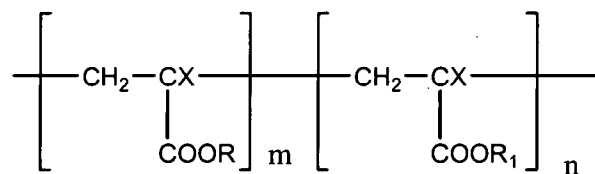
59. (Withdrawn) The method of Claim 58 wherein the implantable medical device is a stent.

60. (Withdrawn) The method of Claim 58 wherein the mass ratio between the structural component and the biobeneficial component is between about 99:1 and about 1:1.

61. (Withdrawn) The method of Claim 58 wherein the mass ratio between the structural component and the biobeneficial component is between about 19:1 and about 9:1.

62. (Withdrawn) The method of Claim 58 wherein the mass ratio between the structural component and the biobeneficial component is about 3:1.

63. (Withdrawn) The method of Claim 58 wherein the acrylic homopolymer or linear acrylic copolymer have the structure:



wherein

- (a) X is hydrogen or methyl group;

- (b) each of R and R₁ is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl;
- (c) m is a positive integer; and
- (d) n is 0 or a positive integer.

64. (Withdrawn) The method of Claim 58 wherein the acrylic homopolymer and linear acrylic copolymer are synthesized by polymerizing monomers selected from a group consisting of methylmethacrylate, ethylmethacrylate, n-propyl methacrylate, iso-propylmethacrylate, n-butylmethacrylate, n-laurylmethacrylate, 2-hydroxyethylmethacrylate, and mixtures thereof.

65. (Withdrawn) The method of Claim 58 wherein the step of preparing the polymeric blend includes synthesizing the biobeneficial random, block, graft or brush copolymers.

66. (Withdrawn) The method of Claim 65 wherein the block copolymers include AB-, ABA-, BAB-, ABC-, or ABCBA-block copolymers.

67. (Withdrawn) The method of Claim 65 wherein the step of synthesizing the block copolymers includes copolymerizing an acrylate and a biobeneficial monomer by a method of living, free-radical copolymerization with initiation-transfer agent termination of the living macro chains.

68. (Withdrawn) The method of Claim 67 wherein the acrylate is methylmethacrylate, ethylmethacrylate, n-propyl methacrylate, iso-propylmethacrylate, n-butylmethacrylate, n-laurylmethacrylate, 2-hydroxyethylmethacrylate, or mixtures thereof.

69. (Withdrawn) The method of Claim 67 wherein the biobeneficial monomer includes acryloyl-, methacryloyl-, vinyl, or allyl-modified adducts of superoxide dismutase-mimetics;

acryloyl-, methacryloyl-, vinyl, or allyl-modified diazenium diolate type nitric oxide donors; or acryloyl-, methacryloyl-, vinyl, or allyl-modified polycationic peptides.

70. (Withdrawn) The method of Claim 67 wherein the biobeneficial monomer is 2-acrylamido-2-methyl-1-propanesulfonic acid, poly(ethylene glycol) methacrylate, 3-sulfopropyl acrylate, 3-sulfopropyl acrylate methacrylate, N-vinylpyrrolidone, vinyl sulfonic acid, 4-styrene sulfonic acid, or 3-allyloxy-2-hydroxypropanesulfonic acid.

71. (Withdrawn) The method of Claim 58 wherein the biobeneficial moiety includes fragments derived from poly(alkylene glycols), superoxide dismutase-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

72. (Withdrawn) The method of Claim 71 wherein the poly(alkylene glycols) are poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), poly(ethylene glycol-co-propylene glycol), poly(ethylene oxide-co-propylene oxide), or mixtures thereof.

73. (Withdrawn) The method of Claim 71 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

74. (Withdrawn) The method of Claim 71 wherein the polysaccharides are heparin, heparin derivatives, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

75. (Withdrawn) The method of Claim 74 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

76. (Withdrawn) The method of Claim 75 wherein the heparin salts are sodium heparin, potassium heparin, lithium heparin, calcium heparin, magnesium heparin, ardeparin sodium, or mixtures thereof.

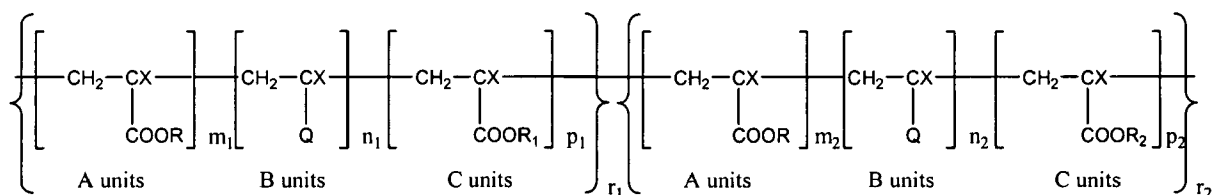
77. (Withdrawn) The method of Claim 71 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropane sulfonic acid, or mixtures thereof.

78. (Withdrawn) The method of Claim 58 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 99:1 and about 1:1.

79. (Withdrawn) The method of Claim 58 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 19:1 and about 9:1

80. (Withdrawn) The method of Claim 58 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is about 3:1.

81. (Withdrawn) The method of Claim 58 wherein the copolymer comprising the biobeneficial component has the formula:



wherein

(a) $m_1, n_1, p_1, r_1, m_2, n_2, p_2$, and r_2 are all integers;

(b) $m_1 \geq 0, n_1 > 0, p_1 \geq 0, r_1 > 0; m_2 \geq 0, n_2 > 0, p_2 \geq 0, r_2 > 0$; and

(c)

- (i) if $m_1 = 0$, then $p_1 > 0$;
- (ii) if $p_1 = 0$, then $m_1 > 0$; and
- (iii) if $m_2 = 0$, then $p_2 > 0$; and
- (iv) if $p_2 = 0$, then $m_2 > 0$; and
- (v) r_1 and r_2 are the same or different;
- (vi) m_1 and m_2 are the same or different;
- (vii) n_1 and n_2 are the same or different; and
- (viii) p_1 and p_2 are the same or different;

(d) X is hydrogen or methyl group;

(e) each of R and R_1 , independently, is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and

(f) Q is a fragment providing the copolymer with biobeneficial properties.

82. (Withdrawn) The method of Claim 58 wherein the copolymer comprising the biobeneficial component is poly(ethylene glycol)-block-poly(n-butylmethacrylate)-block-poly(ethylene glycol), poly(n-butylmethacrylate)-block-poly(ethylene glycol)-block-poly(n-butylmethacrylate), or mixtures thereof.

REMARKS

Claims 1-82 are restricted into Group I, claims 1-30; Group II, claim 31-57; and Group III, claims 58-82.

Applicant elects Group II, claims 31-57, for prosecution without traverse.

Applicant elects poly(n-butylmethacrylate) (PBMA) as the species of the genus structural component for examination. Claims 31-49 and 51-57 read upon this species.

Applicant further elects poly(ethylene glycol)-co-PBMA-co-poly(ethylene glycol) (PEG-PBMA-PEG) as the species of the genus biobeneficial component for examination. Claims 31-49 and 51-57 read upon all read upon this species.

The undersigned authorizes the examiner to charge any fees that may be required or credit of any overpayment to be made to Deposit Account No. 07-1850.

CONCLUSION

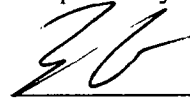
If the Examiner has any questions or concerns, the Examiner is invited to telephone the undersigned attorney at (415) 393-9885.

The undersigned authorizes the examiner to charge any fees that may be required or credit of any overpayment to be made to Deposit Account No. 07-1850.

Date: August 13, 2007

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Respectfully submitted,



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Reg. No. 46,872



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/815,421

03/31/2004

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50623.359

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10/12/2007

DOCKETED: Response due:
1/12/08

OCT 15 2007

BY: AV Atty: ZL
SQUIRE, SANDERS & DEMPSEY

EXAMINER

SILVERMAN, ERIC E

ART UNIT

PAPER NUMBER

1615

MAIL DATE

DELIVERY MODE

10/12/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/815,421

Applicant(s)

HOSSAINY, SYED F.A.

Examiner

Eric E. Silverman, PhD

Art Unit

1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-82 is/are pending in the application.
- 4a) Of the above claim(s) 1-30, 42-46, 50 and 53-82 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31-41, 47-49, 51 and 52 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 10-12-04.
- 4) ☒ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION***Election/Restrictions***

Applicants' response to the election/restriction requirement was received and entered on 8/13/2007. Applicants' elected Group II, claims 31 – 57 without traverse. Applicants further elected PBMA as the species of structural component and PEG-PBMA-PEG as the biobeneficial component. Applicants aver that claims 31 – 49 and 51 – 57 read on the elected species. Since no error was alleged in the election requirement, the election of species is deemed to be **without traverse**. Note that the claims set entered 8/13/2007 incorrectly uses the status modifier "original" for claim 50. Future claim sets should indicate this claim to as "withdrawn".

Claims 42 – 46 and 53 – 57 do not read on the elected species. The elected biobeneficial component, PEG-PBMA-PEG does not contain any of the peptides of claim 42, nor the polysaccharides of claim 43 – 45, nor the sulfonic acid derivatives of claim 46. Nor does the elected species include the structure of claim 52, upon which claims 53 – 57 depend. Examiner contacted Applicants representative on 9/17/2007 in an attempt to reach an agreement about the status of these claims. See the attached interview summary for details of the conversation. No agreement was reached, however, because claims 42 – 46 and 53 – 57 do not read on the elected species, these claims are nonetheless withdrawn from consideration.

Future claim listings should indicate the withdrawal of claims 42 – 46, 50, and 53 – 57.

Priority

It is noted that this Application claims benefit of copending US Application No. 10/317,435, filed 12/11/2002. However, the copending application does not have support for the elected PEG-PBMA-PEG biobeneficial agent. Accordingly, the actual filing date of this application, 3/31/2004, is the effective filing date.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39 – 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 states, in pertinent part, “AB-, ABA-, BAB-, ABC-, or ABCBA- block copolymers.” It is unclear what is meant by the dash in this notation. For example, it is not clear how an “AB-” block copolymer is different from an “AB” block copolymer.

In claim 40, it is not clear what is encompassed by “fragments derived from poly(alkylene glycols)”, nor is it clear what is included in “derivatives of sulfonic acid”. The artisan would not know what fragments are “derived from” or are “derivatives of” the named compounds, and thus would be unable to determine the metes and bounds of the claimed invention.

Claim 41 lacks antecedent basis for “the poly(alkylene glycols)” in claim 40. Claim 40 recites “fragments derived from poly(alkylene glycols)”.

Claim Rejections - 35 USC § 103

Art Unit: 1615

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 31 – 41, 47 – 49, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,110,483 to Whitbourne et al. in view of WO 2004/101018, of record.

I. Claim interpretation

It is recognized that Applicants may be their own lexicographer. In the instant application, Applicants have used an unusual definition for block copolymers. In the discussion of the nature of the copolymer blocks (pages 4 – 5 of the specification), Applicants explicitly state “The[se] blocks *need not be linked at the ends*, . . .” (emphasis added).

Using Applicants’ definition, a physical mixture of the homopolymers corresponding to the various blocks of a block copolymer is a block copolymer where the blocks are not linked at the ends.

While it is recognized that this is not the typical definition of a block copolymer in the art, Applicants’ right to be his or her own lexicographer is not abridged so long as the atypical definition is clear so as to put readers on notice. In this case, the definition is clear, and readers are put on notice, as to the atypical use of the term “block copolymer”.

II. Reason for the rejection

The claims require a medical device, specifically a stent, with a two-part coating. The coating must contain a structural component, for which Applicants elected PBMA (poly (butyl methacrylate)), and a biobeneficial component, for which Applicants elected PEG-PBMA-PEG. Dependent claims specify the ratio of the two components.

Whitbourne teaches stents coated with PBMA (claim 7).

Whitbourne does not teach the use of PEG-PBMA-PEG.

The WO reference teaches the use of PBMA and PEG as a topcoat for a polymer coated stent (examples 4 and 5). The PEG and PBMA form an interpenetrating polymer mixture, which suffices to read on the elected PEG-PBMA-PEG block copolymer according to Applicants' definition of block copolymer in the instant specification. The topcoat has the advantage of providing a controllable release of a drug in the stent (see Fig. 4, description thereof, and examples).

It would be prime facie obvious to a person of ordinary skill in the art at the time of the invention to use the topcoat composition of WO on the PBMA coated stent of Witbourne. The motivation is to control the drug release rate. With regard to the ratio of components, this is a matter of mere optimization, wherein the artisan would find the best ratio depending on the desired use. Since WO teaches how to make and provide the topcoat to a stent, the artisan would enjoy a reasonable expectation of success.

Conclusion

No claims are allowed.


Art Unit: 1615

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric E. Silverman, PhD whose telephone number is 571 272 5549. The examiner can normally be reached on Monday to Friday 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571 272 8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric E. Silverman, PhD
Art Unit 1615


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Applicant

Syed F.A. Hossainy

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1614

U.S. PATENT DOCUMENTS


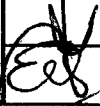
Examiner Initial	Ref. No.	Document Number	Date of Patent	Name	Class	Subclass	Filing Date if Appropriate
CA	A1	2,072,303	3/2/37	Herrmann et al.	128	335.5	10/14/33
	A2	2,386,454	10/9/45	Frosch et al.	260	78	11/22/40
	A3	3,773,737	11/20/73	Goodman et al.	260	78	6/9/71
	A4	3,849,514	11/19/74	Gray, Jr. et al.	260	857	9/5/69
	A5	4,226,243	10/7/80	Shalaby et al.	128	335.5	7/27/79
	A6	4,329,383	5/11/82	Joh	428	36	7/21/80
	A7	4,343,931	8/10/82	Barrows	528	291	12/17/79
	A8	4,529,792	7/16/85	Barrows	528	291	5/6/82
	A9	4,611,051	9/9/86	Hayes et al.	528	295.3	12/31/85
	A10	4,656,242	4/7/87	Swan et al.	528	295.3	6/7/85
	A11	4,733,665	3/29/88	Palmaz	128	343	11/7/85
	A12	4,800,882	1/31/89	Gianturco	128	343	3/13/87
	A13	4,882,168	11/21/89	Casey et al.	424	468	9/5/86
	A14	4,886,062	12/12/89	Wiktor	128	343	10/19/87
	A15	4,931,287	6/5/90	Bae et al.	424	484	6/14/88
	A16	4,941,870	7/17/90	Okada et al.	600	36	12/30/88
	A17	4,977,901	12/18/90	Ofstead	128	772	4/6/90
	A18	5,019,096	5/28/91	Fox, Jr. et al.	623	1	10/14/88
	A19	5,100,992	3/31/92	Cohn et al.	424	501	5/3/90
	A20	5,112,457	5/12/92	Marchant	204	165	7/23/90
	A21	5,133,742	7/28/92	Pinchuk	623	1	11/14/91
	A22	5,163,952	11/17/92	Froix	623	1	9/14/90
	A23	5,165,919	11/24/92	Sasaki et al.	424	488	9/26/90
	A24	5,219,980	6/15/93	Swidler	528	272	4/16/92
	A25	5,258,020	11/2/93	Froix	623	1	4/24/92
	A26	5,272,012	12/21/93	Opolski	428	423.1	1/29/92

	A27	5,292,516	3/8/94	Viegas et al.	424	423	11/8/91
	A28	5,298,260	3/29/94	Viegas et al.	424	486	6/9/92
	A29	5,300,295	4/5/94	Viegas et al.	424	427	9/13/91
	A30	5,306,501	4/26/94	Viegas et al.	424	423	11/8/91
	A31	5,306,786	4/26/94	Moens et al.	525	437	12/16/91
	A32	5,328,471	7/12/94	Slepien	604	101	8/4/93
	A33	5,330,768	7/19/94	Park et al.	424	501	7/5/91
	A34	5,380,299	1/10/95	Fearnott et al.	604	265	8/30/93
	A35	5,417,981	5/23/95	Endo et al.	424	486	4/28/93
	A36	5,447,724	9/5/95	Helmus et al.	424	426	11/15/93
	A37	5,455,040	10/3/95	Marchant	424	426	11/19/92
	A38	5,462,990	10/31/95	Hubbell et al.	525	54.1	10/5/93
	A39	5,464,650	11/7/95	Berg et al.	427	2.30	4/26/93
	A40	5,485,496	1/16/96	Lee et al.	378	64	9/22/94
	A41	5,516,881	5/14/96	Lee et al.	528	320	8/10/94
	A42	5,569,463	10/29/96	Helmus et al.	424	426	6/7/95
	A43	5,578,073	11/26/96	Haimovich et al.	623	1	9/16/94
	A44	5,584,877	12/17/96	Miyake et al.	623	1	6/23/94
	A45	5,605,696	2/25/97	Eury et al.	424	423	3/30/95
	A46	5,607,467	3/4/97	Froix	623	1	6/23/93
	A47	5,609,629	3/11/97	Fearnott et al.	623	1	6/7/95
	A48	5,610,241	3/11/97	Lee et al.	525	411	5/7/96
	A49	5,616,338	4/1/97	Fox, Jr. et al.	424	423	4/19/91
	A50	5,624,411	4/29/97	Tuch	604	265	6/7/95
	A51	5,628,730	5/13/97	Shapland et al.	604	21	7/18/94
	A52	5,644,020	7/1/97	Timmermann et al.	528	288	5/10/96
	A53	5,649,977	7/22/97	Campbell	623	1	9/22/94
	A54	5,658,995	8/19/97	Kohn et al.	525	432	11/27/95
	A55	5,667,767	9/16/97	Greff et al.	424	9.411	7/27/95
	A56	5,670,558	9/23/97	Onishi et al.	523	112	7/6/95
	A57	5,674,242	10/7/97	Phan et al.	606	198	11/15/96
	A58	5,679,400	10/21/97	Tuch	427	2.14	6/7/95
	A59	5,700,286	12/23/97	Tartaglia et al.	623	1	8/22/96

	A60	5,702,754	12/30/97	Zhong	427	2.12	2/22/95
	A61	5,711,958	1/27/98	Cohn et al.	424	423	7/11/96
	A62	5,716,981	2/10/98	Hunter et al.	514	449	6/7/95
	A63	5,721,131	2/24/98	Rudolph et al.	435	240	4/28/94
	A64	5,723,219	3/3/98	Kolluri et al.	428	411.1	12/19/95
	A65	5,735,897	4/7/98	Buirge	623	12	1/2/97
	A66	5,746,998	5/5/98	Torchilin et al.	424	9.4	8/8/96
	A67	5,759,205	6/2/98	Valentini	623	16	1/20/95
	A68	5,776,184	7/7/98	Tuch	623	1	10/9/96
	A69	5,783,657	7/21/98	Pavlin et al.	528	310	10/18/96
	A70	5,788,979	8/4/98	Alt et al.	424	426	2/10/97
	A71	5,800,392	9/1/98	Racchini	604	96	5/8/96
	A72	5,820,917	10/13/98	Tuch	427	2.1	6/7/95
	A73	5,824,048	10/20/98	Tuch	623	1	10/9/96
	A74	5,824,049	10/20/98	Ragheb et al.	623	1	10/31/96
	A75	5,830,178	11/3/98	Jones et al.	604	49	10/11/96
	A76	5,837,008	11/17/98	Berg et al.	623	1	4/27/95
	A77	5,837,313	11/17/98	Ding et al.	427	2.21	6/13/96
	A78	5,849,859	12/15/98	Acemoglu	528	271	3/23/93
	A79	5,851,508	12/22/98	Greff et al.	424	9.411	2/14/97
	A80	5,854,376	12/29/98	Higashi	528	288	3/11/96
	A81	5,858,746	1/12/99	Hubbell et al.	435	177	1/25/95
	A82	5,865,814	2/2/99	Tuch	604	265	8/6/97
	A83	5,869,127	2/9/99	Zhong	427	2.12	6/18/97
	A84	5,873,904	2/23/99	Ragheb et al.	623	1	2/24/97
	A85	5,876,433	3/2/99	Lunn	623	1	5/29/96
	A86	5,877,224	3/2/99	Brocchini et al.	514	772.2	7/28/95
	A87	5,879,713	3/9/99	Roth et al.	424	489	1/23/97
	A88	5,902,875	5/11/99	Roby et al.	528	310	1/28/98
	A89	5,905,168	5/18/99	Dos Santos et al.	562	590	12/10/93
	A90	5,910,564	6/8/99	Gruning et al.	528	310	12/6/96
	A91	5,914,387	6/22/99	Roby et al.	528	310	1/28/98
	A92	5,919,893	7/6/99	Roby et al.	525	411	1/28/98

A93	5,925,720	7/20/99	Kataoka et al.	525	523	12/18/97
A94	5,932,299	8/3/99	Katoot	427	508	4/22/97
A95	5,955,509	9/21/99	Webber et al.	514	772.7	4/23/97
A96	5,958,385	9/28/99	Tondeur et al.	424	61	9/28/95
A97	5,962,138	10/5/99	Kolluri et al.	428	411.1	11/24/97
A98	5,971,954	10/26/99	Conway et al.	604	96	1/29/97
A99	5,980,928	11/9/99	Terry	424	427	7/29/97
A100	5,980,972	11/9/99	Ding	427	2.24	9/22/97
A101	5,997,517	12/7/99	Whitbourne	604	265	1/27/97
A102	6,010,530	1/4/00	Goicoechea	623	1	2/18/98
A103	6,011,125	1/4/00	Lohmeijer et al.	525	440	9/25/98
A104	6,015,541	1/18/00	Greff et al.	424	1.25	11/3/97
A105	6,033,582	3/7/00	Lee et al.	216	37	1/16/98
A106	6,034,204	3/7/00	Mohr et al.	528	328	8/7/98
A107	6,042,875	3/28/00	Ding et al.	427	2.24	3/2/99
A108	6,051,576	4/18/00	Ashton et al.	514	255	1/29/97
A109	6,051,648	4/18/00	Rhee et al.	525	54.1	1/13/99
A110	6,054,553	4/25/00	Groth et al.	528	335	11/12/96
A111	6,056,993	5/2/00	Leidner et al.	427	2.25	4/17/98
A112	6,060,451	5/9/00	DiMaio et al.	514	13	3/20/95
A113	6,060,518	5/9/00	Kabanov et al.	514	781	8/16/96
A114	6,080,488	6/27/00	Hostettler et al.	428	423.3	3/24/98
A115	6,096,070	8/1/00	Ragheb et al.	623	1	5/16/96
A116	6,099,562	8/8/00	Ding et al.	623	1.46	12/22/97
A117	6,110,188	8/29/00	Narciso, Jr.	606	153	3/9/98
A118	6,110,483	8/29/00	Whitbourne et al.	424	423	6/23/97
A119	6,113,629	9/5/00	Ken	623	1.1	5/1/98
A120	6,120,491	9/19/00	Kohn et al.	604	502	4/7/98
A121	6,120,536	9/19/00	Ding et al.	623	1.43	6/13/96
A122	6,120,788	9/19/00	Barrows	424	426	10/16/98
A123	6,120,904	9/19/00	Hostettler et al.	428	423.3	5/24/99
A124	6,121,027	9/19/00	Clapper et al.	435	180	8/15/97
A125	6,129,761	10/10/00	Hubbell	623	11	6/7/95

A126	6,136,333	10/24/00	Cohn et al.	424	423	7/11/97
A127	6,143,354	11/7/00	Koulik et al.	427	2.24	2/8/99
A128	6,153,252	11/28/00	Hossainy et al.	427	2.3	4/19/99
A129	6,159,978	12/12/00	Myers et al.	514	252.1	11/24/98
A130	6,165,212	12/26/00	Dereume et al.	623	1.13	6/28/99
A131	6,172,167	1/9/01	Stapert et al.	525	420	6/27/97
A132	6,177,523	1/23/01	Reich et al.	525	459	7/14/99
A133	6,180,632	1/30/01	Myers et al.	514	252.1	11/24/98
A134	6,203,551	3/20/01	Wu	606	108	10/4/99
A135	6,211,249	4/3/01	Cohn et al.	514	772.1	1/13/98
A136	6,214,901	4/10/01	Chudzik et al.	523	113	4/15/99
A137	6,231,600	5/15/01	Zhong	623	1.42	5/26/99
A138	6,240,616	6/5/01	Yan	29	527.2	4/15/97
A139	6,245,753	6/12/01	Byun et al.	514	56	4/27/99
A140	6,245,760	6/12/01	He et al.	514	234.8	11/24/98
A141	6,248,129	6/19/01	Froix	623	1.42	10/23/98
A142	6,251,136	6/26/01	Guruwaiya et al.	623	1.46	12/8/99
A143	6,254,632	7/3/01	Wu et al.	623	1.15	9/28/00
A144	6,258,121	7/10/01	Yang et al.	623	1.46	7/2/99
A145	6,258,371	7/10/01	Koulik et al.	424	422	4/3/98
A146	6,262,034	7/17/01	Mathiowitz et al.	514	44	11/25/97
A147	6,270,788	8/7/01	Koulik et al.	424	423	10/4/99
A148	6,277,449	8/21/01	Kolluri et al.	427	289	6/30/99
A149	6,283,947	9/4/01	Mirzaee	604	264	7/13/99
A150	6,283,949	9/4/01	Roorda	604	288.02	12/27/99
A151	6,284,305	9/4/01	Ding et al.	427	2.28	5/18/00
A152	6,287,628	9/11/01	Hossainy et al.	427	2.3	9/3/99
A153	6,299,604	10/9/01	Ragheb et al.	604	265	8/20/99
A154	6,306,176	10/23/01	Whitbourne	623	23.59	9/21/99
A155	6,331,313	12/18/01	Wong et al.	424	427	10/22/99
A156	6,335,029	1/1/02	Kamath et al.	424	423	12/3/98
A157	6,344,035	2/5/02	Chudzik et al.	604	265	10/20/00

	A158	6,346,110	2/12/02	Wu	606	108	1/3/01
	A159	6,358,556	3/19/02	Ding et al.	427	2.24	1/23/98
	A160	6,379,381	4/30/02	Hossainy et al.	623	1.42	9/3/99
	A161	6,387,379	5/14/02	Goldberg et al.	424	400	2/28/94
	A162	6,395,326	5/28/02	Castro et al.	427	2.24	5/31/00
	A163	6,419,692	7/16/02	Yang et al.	623	1.15	2/3/99
	A164	6,451,373	9/17/02	Hossainy et al.	427	2.25	8/4/00
	A165	6,482,834	11/19/02	Spada et al.	514	311	4/6/01
	A166	6,494,862	12/17/02	Ray et al.	604	96.01	12/30/99
	A167	6,503,538	1/7/03	Chu et al.	424	497	8/30/00
	A168	6,503,556	1/7/03	Harish et al.	427	2.24	12/28/00
	A169	6,503,954	1/7/03	Bhat et al.	514	772.2	7/21/00
	A170	6,506,437	1/14/03	Harish et al.	427	2.25	10/17/00
	A171	6,524,347	2/25/03	Myers et al.	2514	252.1	9/29/00
	A172	6,527,801	3/4/03	Dutta	623	1.46	4/13/00
	A173	6,527,863	3/4/03	Pacetti et al.	118	500	6/29/01
	A174	6,528,526	3/4/03	Myers et al.	214	311	9/29/00
	A175	6,530,950	3/11/03	Alvarado et al.	623	1.13	8/3/00
	A176	6,530,951	3/11/03	Bates et al.	623	1.45	10/23/97
	A177	6,540,776	4/1/03	Sanders Millare et al.	623	1.15	12/28/00
	A178	6,544,223	4/8/03	Kokish	604	103.01	1/5/01
	A179	6,544,543	4/8/03	Mandrusov et al.	424	422	12/27/00
	A180	6,544,582	4/8/03	Yoe	427	2.24	1/5/01
	A181	6,555,157	4/29/03	Hossainy	427	2.24	7/25/00
	A182	6,558,733	5/6/03	Hossainy et al.	427	2.24	10/26/00
	A183	6,565,659	5/20/03	Pacetti et al.	118	500	6/28/01
	A184	6,572,644	6/3/03	Moein	623	1.11	6/27/01
	A185	6,585,755	7/1/03	Jackson et al.	623	1.15	6/29/01
	A186	6,585,765	7/1/03	Hossainy et al.	623	1.45	6/29/00
	A187	6,585,926	7/1/03	Mirzaee	264	400	8/31/00
	A188	6,605,154	8/12/03	Villareal	118	500	5/31/01



A189	6,616,765	9/9/03	Hossaony et al.	623	1.45	1/10/02
A190	6,623,448	9/23/03	Slater	604	95.01	3/30/01
A191	6,625,486	9/23/03	Lundkvist et al.	604	21	4/11/01
A192	6,645,135	11/11/03	Bhat	600	3	3/30/01
A193	6,645,195	11/11/03	Bhat et al.	604	528	1/5/01
A194	6,656,216	12/2/03	Hossainy et al.	623	1.13	6/29/01
A195	6,656,506	12/2/03	Wu et al.	424	489	5/9/01
A196	6,660,034	12/9/03	Mandrusov et al.	623	1.42	4/30/01
A197	6,663,662	12/16/03	Pacetti et al.	623	1.13	12/28/00
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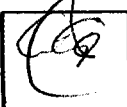
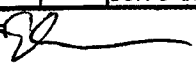
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EXAMINER: Initial if references considered, whether or not citation is in conformance with MPEP § 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.		

Interview Summary	Application No. 10/815,421	Applicant(s) HOSSAINY, SYED F.A.	
	Examiner Eric E. Silverman, PhD	Art Unit 1615	

All participants (applicant, applicant's representative, PTO personnel):

(1) Eric E. Silverman, PhD. (3) _____.

(2) Zhaoyang Li. (4) _____.

Date of Interview: 17 September 2007.

Type: a) ☒ Telephonic b) ☐ Video Conference
c) ☐ Personal [copy given to: 1) ☐ applicant 2) ☐ applicant's representative]

Exhibit shown or demonstration conducted: d) ☐ Yes e) ☒ No.
If Yes, brief description: _____.

Claim(s) discussed: of record.

Identification of prior art discussed: of record.

Agreement with respect to the claims f) ☐ was reached. g) ☒ was not reached. h) ☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Examiner requested clarification as to which claims read on the elected species. Examiner indicated that claims 42 - 46 and 53 - 57 do not appear to read on the elected species. Applicants' representative disagreed. The discussion did not produce an agreement in this matter. Examiner indicated that prosecution would proceed, with an appropriate action to follow, irrespective of the disagreement.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiner's Amendment, no separate Interview Summary Record is required.

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- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
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	Examiner Eric E. Silverman, PhD		Art Unit 1615	Page 1 of 1

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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,110,483	08-2000	Whitbourne et al.	424/423
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action . (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.



US006110483A

United States Patent [19]

Whitbourne et al.

[11] **Patent Number:** **6,110,483**
 [45] **Date of Patent:** ***Aug. 29, 2000**

[54] **ADHERENT, FLEXIBLE HYDROGEL AND MEDICATED COATINGS**

[75] Inventors: **Richard J. Whitbourne**, Fairport;
Xianping Zhang, Webster, both of N.Y.

[73] Assignee: **STS Biopolymers, Inc.**, Henrietta, N.Y.

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **08/880,512**

[22] Filed: **Jun. 23, 1997**

[51] **Int. Cl.⁷** **A61F 2/02**

[52] **U.S. Cl.** **424/423**; 424/94.64; 424/78.24; 424/78.27; 514/834; 514/781; 623/1; 623/3; 604/187; 604/313; 604/319; 427/2.3; 427/569; 427/421; 427/429; 427/430.1

[58] **Field of Search** 424/423, 94.64, 424/78.24, 78.27; 514/834, 781; 623/1, 3, 900; 604/187, 313, 319; 427/2.3, 569, 421, 429, 430.1

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Primary Examiner—Michael A. Williamson

Attorney, Agent, or Firm—Michael A. Gollin; Venable

[57] **ABSTRACT**

The adherent coating of the invention comprises a stabilizing polymer together with an active agent (a hydrophilic polymer and/or a bioactive agent) in a layer bonded to the surface of a medical device. This invention encompasses the coating liquids used for coating medical devices, methods of coating the devices, and the coated devices. The stabilizing polymer is selected to entrap the active agent in a coating that has a high degree of flexibility and has improved bonding to a wide variety of substrates. Preferred stabilizing polymers are cross-linkable acrylic and methacrylic polymers, ethylene acrylic acid copolymers, styrene acrylic copolymers, vinyl acetate polymers and copolymers, vinyl acetal polymers and copolymers, epoxy, melamine, other amino resins, phenolic polymers, copolymers thereof, and combinations.

40 Claims, No Drawings

ADHERENT, FLEXIBLE HYDROGEL AND MEDICATED COATINGS

BACKGROUND OF THE INVENTION

This invention relates to coatings for biomedical devices in which an active agent is entrapped in a stabilizing polymer that provides improved bonding and flexibility. The active agent may be a hydrophilic polymer that produces a lubricious hydrogel, a bioactive agent that confers a physiological effectiveness, or a combination, so that the coating may be a hydrogel and/or a medicated coating.

Known lubricious coatings that may be applied to biomedical devices include coatings of polyvinylpyrrolidone (PVP), polyurethane, acrylic polyester, vinyl resin, fluorocarbons, silicone, rubber, and some combinations. Whitbourne, U.S. Pat. No. 5,001,009, relates to a hydrophilic coating containing PVP and cellulose ester polymers. Whitbourne, U.S. Pat. No. 5,525,348 discusses medicated polymer coatings based on cellulose esters.

Known hydrogel and medicated coatings for insertable devices have disadvantages, including poor adherence to inert polyolefin and metal surfaces, too much friction, too little permanence, and difficult or hazardous methods of application. With polyurethane-PVP coatings, little control can be exerted over the degree of lubricity and resistance to wet abrasion of the coatings, and such coatings are often unstable. PVP-cellulose ester coatings may be brittle, and are difficult to bond to certain substrates. Hydrogels can absorb several times their weight in water when placed in an aqueous environment, resulting in water penetrating to the coating/substrate interface, which makes adhesion failure a serious problem.

In order to solve these problems an improved polymer blend is needed for a coating for a medical device which may be formed as a hydrogel and/or a medicated coating, bonds well when dry, resists wet abrasion, is flexible enough to remain coherent on flexible devices, provides improved adherence to a wide variety of substrates, and can be prepared from chemically stable and biocompatible solvents.

SUMMARY OF THE INVENTION

The adherent coatings of the invention comprise a stabilizing polymer in which an active agent is entrapped, the active agent being a hydrophilic polymer and/or a bioactive agent, and the coating being flexible and bonded to the surface of a medical device. This invention encompasses the coating liquids used for coating medical devices, methods of coating the devices, and the coated devices. The coating layer may be formed of a single coating application or successive applications of the coating components.

The invention satisfies a long felt need for more flexible, adherent hydrogel and medicated coatings for insertable medical devices. The invention succeeds where previous efforts at providing such coatings have failed, despite extensive efforts in a crowded and mature art. The invention eliminates the need for cellulose esters, polyurethane, and other coating polymers employed in the prior art, with good resistance to wet abrasion, and enhanced flexibility and adhesion. The materials and methods of the invention were not previously known or suggested, and their advantages were not previously appreciated.

The invention encompasses a coating applied to a surface of a medical device, the coating comprising: (a) a stabilizing polymer selected from the group consisting of cross-linkable

acrylic and methacrylic polymers, ethylene acrylic acid copolymers, styrene acrylic copolymers, vinyl acetate polymers and copolymers, vinyl acetal polymers and copolymers, epoxy, melamine, other amino resins, phenolic polymers, copolymers thereof, and combinations; and (b) an active agent selected from the group consisting of a hydrophilic polymer selected to interact with the stabilizing polymer so as to produce a lubricious hydrogel, and a bioactive agent, and a combination; the active agent being entrapped in the stabilizing polymer such that the coating adheres to the surface when dry and wet, and remains coherent despite flexing of the surface.

Preferably, the stabilizing polymer is cross-linkable and the coating comprises a cross-linker for the stabilizing polymer, such as epoxy resin, melamine resin, other amino resin, and phenolic resin. The stabilizing polymer may be selected from a carboxyl function acrylic polymer, hydroxyl function acrylic polymer, amine function acrylic polymer, methylol function, and amide function acrylic polymer. It may be a cross-linkable acrylic selected from methylmethacrylate, butylmethacrylate, isobutylmethacrylate, ethylmethacrylate, methylacrylate, ethylacrylate, acrylic acid, methacrylic acid, styrene methacrylate, and styrene acrylate, and copolymers thereof.

The surface of the medical device preferably comprises a material selected from the group consisting of stainless steel, nickel, gold, chrome, nickel titanium alloy, platinum, another metal, silicone, polyethylene, other polyolefins, polyesters, other plastics, glass, polyurethane, acetal, polyamide, and polyvinyl chloride.

The medical device may be chosen from any insertable or partially insertable device for invasive or similar procedures, such as needles, guide wires, catheters, surgical instruments, equipment for endoscopy, wires, stents, angioplasty balloons, wound drains, wound dressings, arteriovenous shunts, gastroenteric tubes, urethral inserts, laparoscopic equipment, pellets, and implants.

The bioactive agent is preferably selected from the group consisting of a pharmaceutical agent, a salt, an osmotic agent, and DNA. The coating may comprise a surfactant, a colorant, or plasticizer(s).

The stabilizing polymer may be concentrated in an inner layer and the active agent in an outer layer. In preferred embodiments, the coating thickness is less than about 50 microns, the active agent is a hydrophilic polymer and the coating is a hydrogel, optionally with a bioactive agent.

The coating resists wet abrasion and remains coherent without cracks despite flexing when applied to difficult to coat inert surfaces such as stainless steel. The selection of stabilizing polymer may be independent of whether the stabilizing polymer is present in the substrate.

A method according to the invention applies a coating to a medical device having an inert surface by applying to the surface a coating liquid comprising a stabilizing polymer and a coating liquid comprising an active agent and drying to remove liquids such that the active agent is entrapped in the stabilizing polymer and the coating adheres to the surface when dry and wet, and remains coherent despite flexing of the surface. A single or multiple coating liquids may contain the stabilizing polymer and the active agent or agents. The liquids may be applied by dipping, spraying, brushing, or wiping, or other methods known in the art. The device surface may be pretreated by gas plasma or other ionizing treatment before the applying step, and/or a precoat layer may be applied. The drying typically comprises heating the coating to at least about 50° C.

When the medical device surface includes one of the stabilizing polymers of the invention, the coating may be prepared by applying a coating liquid comprising a solvent capable of attacking the device surface, and an active agent such that the active agent is entrapped in the surface polymer and the coating adheres to the surface when dry and wet, and remains coherent despite flexing of the medical device.

A kit according to the invention comprises a liquid comprising the stabilizing polymer and a liquid comprising the active agent, the liquids being the same or separate, and the stabilizing polymer and the active agent being selected to produce on the medical device a coherent flexible coating that has wet and dry adhesion. If the liquids are separate, the liquid comprising the active agent preferably comprises a cross-linker for the stabilizing polymer. The liquid or liquids may be based on a solvent selected from the group consisting of water, xylene, tetrahydrofuran, cyclohexanone, ethanol, butyrolactone, butanol, trichloroacetic acid, benzyl alcohol, isobutyl acetate, methyl ethyl ketone, Aromatic 150, toluene, and butyl cellosolve. The stabilizing polymer liquid may be an aqueous cross-linkable acrylic dispersion.

The stabilizing polymer is preferably a water-insoluble polymer that does not significantly react with the hydrophilic polymer or bioactive agent in solution, has low water absorption, provides a high degree of flexibility, and has improved bonding to a wide variety of substrates. Suitable commercial products that may be used in the invention include acrylics such as ACRYLOID® (Rohm & Haas) AT-63, AT-51, AT-81, WR-97; ethylene acrylic acid copolymers such as PRIMACOR™ (DOW) 5989, 5990; melamine resins such as CYMELO® hexamethoxymethylmelamine (CYTEC Industries) 303, 370, 380; epoxies such as EPON (Shell) 1001; and polyvinylbutyral such as BUTVAR B-79 (Monsanto). The preferred acrylic stabilizing polymers include reactive groups such as hydroxyl or carboxyl that can react with epoxies but do not render the polymer hydrophilic.

In one embodiment, the inventive coating includes a hydrophilic polymer such as a water soluble polyolefin such as a hydrophilic vinyl polymer having polar pendant groups, a polyacrylate or methacrylate having hydrophilic esterifying groups, a polyether, a polyethylene glycol, or other polymer with hydrophilic characteristics as known in the art. The hydrophilic polymer is preferably PVP or PVP/vinyl acetate such as PVP/VA (GAF) E-335 and E-635. The stabilizing polymer need not react with the hydrophilic polymer, although in some embodiments of the invention stabilizing polymers are used which can crosslink with themselves thus forming a crosslinked network and entrapping hydrophilic polymer molecules in the crosslinked network. In another embodiment, the coating comprises a bioactive agent in addition to the stabilizing polymer, either instead of or in addition to the hydrophilic polymer. The bioactive agent may be an antithrombogenic, antibacterial, anticancer, gene therapy, or other agent, present in an amount that is effective to achieve the desired effect under the conditions to which the coating is subjected. This generally includes a time release effect attributable to the interaction of the bioactive agents with the stabilizing polymer.

Further objectives and advantages that can be attained by the present invention will become apparent from the detailed description.

DETAILED DESCRIPTION OF THE INVENTION

In describing preferred embodiments of the present invention illustrated in the examples, specific terminology is

employed for the sake of clarity. However, the invention is not intended to be limited to the specific terminology so selected, and it is to be understood that each specific element includes all technical equivalents which operate in a similar manner to accomplish a similar purpose.

The chemical structure and physical characteristics of hydrogels and medicated coatings for medical devices are poorly understood and difficult to predict. Research in this field depends heavily on empirical results as to the performance of particular coating compositions under relevant conditions. Thus, the special advantages of the inventive coatings could not have been appreciated from the prior art.

The coatings of the invention are blends, defined as a mixture so combined as to render the components indistinguishable from each other. Such a coating is a complex structure that may have one or a combination of several physical forms. It is a coating, defined as a material that forms a thin continuous layer over the substrate, and could be referred to as a film. It may be a solid mixture of the stabilizing polymer and hydrophilic polymer or bioactive agent, additives, and possibly solvent residues blended together. Alternatively, the coating may be a complete solid solution, that is a mixture uniformly dispersed throughout the solid phase with homogeneity at the molecular or ionic level, or it may be a combination of dissolved and mixed components, such as a mixture of a polymer coating solution and insoluble particles in suspension. The coating may take the form of a composite, that is a structure composed of a mixture or combination of polymer and other constituents that differ in form and chemical composition and are essentially insoluble in each other. It may be referred to as a matrix of polymer in which other components are entrapped. The coating may comprise separate layers, discrete or intermingled, each of which may have any or several of these forms.

Thus, the structure of the coating is intermingled molecules of the polymer components and other coating components, in a homogeneous distribution with attributes of a solid phase mixture and solution. During drying, the polymers presumably become tangled together and obtain the desired characteristics of a hydrogel or stable matrix capable of sustained release of a bioactive agent. This relationship between the components is referred to as an entrapment of the active agent in the stabilizing polymer, with the result that the active agent is not solubilized or removed directly from the coating, as it would be without the stabilizing polymer, and the coating adheres to the substrate well enough to withstand dry handling and wet conditions expected in use.

The stabilizing polymer according to the invention is non-toxic and physiologically acceptable. Most of the suitable stabilizing polymers dissolve in organic solvents, and they have a poor affinity for water, produce a water-insoluble coating film when applied to a substrate with the other coating components, and adhere to the substrate or a pre-coated substrate under applications involving insertion into tissue and removal. Such a polymer will generally absorb less than about 30%, preferably less than about 10% of its weight in water. The amount and kind of stabilizing polymer must also be adapted to maintain coating integrity during swelling of the coating due to hydration of the hydrophilic polymer. Thus, the stabilizing polymer stabilizes hydrophilic polymers and bioactive agents and renders them entrapped on the coated surface.

The hydrophilic component is non-toxic and physiologically acceptable. It dissolves in organic solvents, and is

partially or totally soluble in water. It absorbs and retains water and swells when wet in conjunction with the other coating components, absorbing at least its own weight in water, preferably more than about five times its weight, most preferably more than about ten times its weight, to produce a hydrogel that is suitably lubricious when wet. The amount and kind of hydrophilic polymer may readily hydrophobed in conjunction with the hydrophobic polymer and hydrating agent to satisfy these criteria. Such hydrophilic polymers are well-known in the art, and a person of ordinary skill can readily find appropriate hydrophilic polymers that are compatible with the stabilizing polymer in the sense that together they form a hydrogel.

The hydrophilic component may be of any of the classes discussed in *Concise Encyclopedia of Polymer Science and Engineering*, Kroschwitz, ed. (Wiley 1990), pp. 458–59, which is incorporated herein by reference. Polymers such as polyvinylpyrrolidone, polyethylene glycol, polyethylene oxide, or polyvinyl alcohol are acceptable, alone or in combination. Examples of suitable hydrophilic polymers include homopolymers or copolymers of the following compounds: polyolefins such as vinyl polymers having polar pendant groups, N-vinylpyrrolidone, N-vinyl lactam, N-vinyl butyrolactam, N-vinyl caprolactam, sodium styrene sulfonate monomer, 2-acrylamido-2-methylpropane sulfonic acid, sodium vinyl sulfonate, vinyl pyridine, acrylates or methacrylates having hydrophilic esterifying groups. Other hydrophilic polymers include polyethers, polyethylene glycol, polysaccharides, hydrophilic polyurethanes, polyhydroxyacrylates, polymethacrylates, and copolymers of vinyl compounds and hydroxyacrylates or acrylic acid, so long as the appropriate hydrophilicity is present. Other examples include dextran, xanthan, hydroxypropyl cellulose, methyl cellulose, polyacrylamide, and polypeptides. Other hydrophilic components are known to persons of skill in the art. The concentration and type of this component in the coating is sufficient to absorb water and become lubricious when wet, while being compatible with the stabilizing polymer component and (if present) the bioactive agent.

The concentration of hydrophilic polymer in the coating is preferably between about 10% and about 98%, most preferably between about 70% and about 90% of the coating or outer sublayer in which it is present. In a multi-layer coating, where the hydrophilic component is present as a top coat, the top coat may also optionally include up to about 10% or more of a hydrophobic polymer. Some stabilizing polymers are less hydrophilic, and contribute some of the stabilizing characteristics defined above for a hydrophobic polymer, and some hydrophobic polymers have higher absorbency of water, so that greater or lesser amounts of the particular components may be desirable to achieve the objects of the invention.

Substrates to which coatings according to the invention may be applied include polyurethane, polyvinylchloride, acetal, polyethylene, polypropylene, polyamide, polyester, silicone, and metals such as stainless steel, platinum, gold, nickel, titanium, nickel-titanium alloys, chrome, and others. The advantages of the inventive coating are particularly evident on stainless steel wires, polyethylene catheters, and other notoriously difficult to coat substrates. Preferred devices include needles, guide wires, catheters, surgical instruments, equipment for endoscopy, wires, stents, angioplasty balloons, wound drains, arteriovenous shunts, gastroenteric tubes, urethral inserts, laparoscopic equipment, pellets, or implants.

Preferred stabilizing polymers are based on the following classes, as defined herein and as would be understood by one

of ordinary skill based on e.g. *Concise Encyclopedia of Polymer Science and Engineering*, Kroschwitz, ed. (Wiley 1990), or *Kirk-Othmer Concise Encyclopedia of Chemical Technology*, (Wiley 1985),

5 Acrylics, e.g. polymers and copolymers of acrylic acid and methacrylic acid and esters thereof, as defined for example in ACRYLOID Thermoplastic Acrylic Ester Resins for Industrial Finishing, Rohm & Haas, Bulletin 82A37 (1987), in particular cross-linkable acrylics with at least one component containing carboxyl, hydroxyl, amide, or methy-
10 lol groups. The following ACRYLOID polymers with functional groups given are preferred: AT-51 (hydroxyl), AT-63 (hydroxyl), AT-81 (carboxyl), and WR-97 (hydroxyl). Cross-linkable acrylic emulsions such as RHOPLEX B-15J (Rohm & Haas), and styrene acrylic emulsions such as AROLOX® 820-W-49 (Reichhold) may also be used.

Amino resins, particularly melamine, and derivatives such as methylated or butylated, including hexamethoxymethylmelamine (HMMM).

20 Phenolic resins.

Epoxy resins, particularly cured epoxy polymers such as EPOTUF® 38-505 (Reichhold), and preferably those cured with polyamide, such as EPOTUF® 37-618 (Reichhold).

25 Vinyl polymers, particularly vinyl acetate, vinyl acetals such as polyvinyl butyral, and ethylene vinyl acetate copolymers.

Other appropriate polymers having the requisite characteristics will be apparent to persons of ordinary skill. The polymers preferably, but not necessarily, contain reactive groups or points of reactivity such as hydroxyls, mono-, di- and tertiary amines, acids such as carboxyl, amides, or other groups which represent points of chemical reactivity. In the case of the acrylics, this is referred to as having a “functionality” that is cross-linkable. The polymers and points of chemical reactivity are able to form attractive forces such as hydrogen bonding toward the medical device surface, and also toward the hydrophilic polymer and/or bioactive agent. Such bonds are very strong, and provide desirable adhesion and flexibility to the coating presumably without requiring covalent, ionic, or other links.

30 Polymers with reactive groups are preferred with substrates like metals. However, polymers lacking such groups such as acrylic or styrene copolymers may also be used effectively.

45 The reactive groups can also react to form a cross-linked matrix or help to form a cross-linked matrix. If desired, cross-linkers such as urea resins, melamines, isocyanates, phenolics, and others may be incorporated to interact with the points of chemical reactivity on the polymer chains to cross-link the polymers of the invention with themselves. Alternatively, cross-linkers may react with themselves as stabilizing polymers to form a cross-linked matrix in which the hydrophilic polymer is enmeshed, resulting in an adherent, flexible coating. Cross-linking is useful in promoting effective adhesion by ensuring that the solvents do not attack and degrade the polymer layer excessively when subsequent layers are applied.

60 Coatings according to the invention may be prepared with polymers that lack points of reactivity, such as acrylic or styrene polymers or copolymers. Likewise, coatings may be made without cross-linking. However, with such coatings a greater coating thickness may be required or desirable than with layers made of polymers with points of reactivity and layers with cross-linking, in order to achieve a high degree of adhesion and flexibility according to the invention. For example, cross-linked coatings with polymers having reac-

tive groups may be about two to about ten microns thick, in contrast with a coating of an acrylic styrene copolymer, with a hydrogel layer on top, and a total thickness of about 30–40 microns.

The coatings of the present invention are extremely durable, even when subjected to adhesion and flexing tests, as shown in the examples. Such enhanced adhesion and flexibility is a surprising result. The coatings according to the invention may be applied to the surface of a biomedical device or other device with sufficient thickness and permanence to retain the coating's desirable qualities throughout the useful life of the coated device. The coatings of the invention are nonreactive with living tissue and are non-thrombogenic in blood.

The coatings of the invention may be thin, on the order of 2 to 100 microns, preferably less than about 50 microns, and coherent in that they form a continuous surface layer. They are resistant to removal on prolonged soaking in aqueous fluids, and are adherent to a wide variety of substrates.

The coatings may be applied by various techniques such as dip, pour, pump, spray, brush, wipe, or other methods known to those skilled in the art. The coating solutions have low viscosities, typically less than 100 CPS, and have good spreading properties. The coatings are preferably baked at elevated temperatures, typically 50° C. to 100° C., to drive off the organic solvents. It may be necessary to treat some surfaces like polyethylene with gas plasma or other ionizing treatment to promote interaction with the coating and adhesion to the substrates.

The coating may contain polymers in addition to the stabilizing polymer such as polyurethane, polyester, styrene polybutadiene, polyvinylidene chloride, polycarbonate, and polyvinyl chloride, preferably in the inner layer to promote adhesion to the surface of the device. The disclosure of U.S. Ser. No. 08/791,440, "Bonding Layers for Medical Device Surface Coatings" is hereby incorporated by reference in its entirety for further enabling details. Such additional polymers are not necessary to achieving the advantages of the invention, in contrast to prior art coatings relying on some of these polymers.

The method of preparing the coatings of the invention employs stable, non-toxic solutions which may be stored and handled with minimal precautions. The method of applying the coating of the invention may comprise preparing a first organic solution of from about 0.01% to about 30% (w/w) of stabilizing polymer, preferably from about 0.2% to about 10%, applying the solution to a substrate surface, and evaporating the solvent, preferably at elevated temperature, then preparing a second solution of from about 0.001% to about 30% (w/w) active agent, preferably from about 0.5% to about 20%, applying it to the treated surface substrate and evaporating the solvents at room or elevated temperature.

The stabilizing polymer solution may also contain from about 0.01% to about 20% of active agent, preferably from about 0.1% to about 5%. The active agent solution may also contain from about 0.01% to about 30% of stabilizing polymer, preferably from about 0.1% to about 10%. Alternatively, the stabilizing polymer and active agent can be prepared in a single solution and applied in a single step.

A plasticizing agent may be included with the stabilizing polymers, in a concentration of from about 0.01% to about 20%, preferably from about 0.1% to about 10% (w/w). The plasticizing agent may be camphor, castor oil, dioctyl phthalate, acetyl tributyl citrate, dibutyl sebacate, sebacic acid, alkyl resin, polyethylene-glycol, polypropylene-glycol,

dibutylphthalate, or other commonly known plasticizers, singly or in combination. The plasticizing agent may be incorporated into the solution of hydrophilic polymer or stabilizing polymer as needed to enhance flexibility of the coating which may be preferable when the object to be coated is likely to bend during use. However, suitable flexibility is achievable according to the invention with coating compositions that lack such additional plasticizers.

Solvents for the stabilizing and adherent polymer include organic solvents such as ketones, esters, toluene, lactones, dimethylformamide, halogenated solvents, tetrahydrofuran, dioxane, amines, glycol butyl ether, alkyl acetates, acetonitrile, and other commonly known organic solvents. The less toxic solvents are preferred. The inclusion of small amounts of hydroxyl groups such as alcohols and moisture in the solvent does not have a significant detrimental effect on the coating and method of the invention. Solvents for the hydrophilic polymer include most of the above as well as alcohols, acetic acid, and like solvents. A solvent system may be selected that is capable of dissolving all the constituents of the coating in a uniform solution, can act as a co-solvent in the coating layer and is non-toxic. If desirable, a solvent may be selected that interacts with the particular substrate surface to promote adhesion.

In one embodiment of the present invention, the article to which the coating is to be applied has a polymer surface comprising the stabilizing polymer, and an "active" solvent is used which obviates the need for the inner layer or base coat by permitting a lubricious hydrophilic layer (or top coat) to be applied directly onto the polymer surface of the article. In this embodiment, the term "active solvent" is defined as a cosolvent for both the polymer or polymer mixture comprising the polymer surface or at least one or more of the polymers in cases of mixed polymer substrates and for the coating polymer(s).

The hydrophilic medicated coatings of this invention are highly lubricious when wetted with an aqueous solution such as body fluid, or a lower alcohol such as ethanol or methanol, yet they are substantially less slippery when dry. Thus, an implant coated according to the invention remains non-slippery for ease of handling and preparation, but becomes lubricious when implanted, so as to protect the patient. The lubricity of the coating can be adjusted within a desirable range from ultra lubricious to not lubricious by adjusting the ratio of the hydrophilic to stabilizing polymers.

A coating according to the invention may be applied to the surface of a biomedical or other device with sufficient thickness and permanence to retain the coating's desirable qualities throughout the useful life of the coated device. The coatings of the invention are non-reactive with living tissue and are non-thrombogenic in blood.

The coatings of the invention have beneficial characteristics for use on the surfaces of devices such as biomedical implants. The coating may be hydrophilic, absorbing water and swelling in an aqueous environment to become a hydrogel, so that the coating has lubricant properties, and is significantly more slippery when wet than when dry.

Various physiologically active agents may be incorporated into the hydrogel coating. Such agents may be incorporated in order to ameliorate certain problems which typically occur on the surfaces of implanted medical devices. For instance, antithrombogenics such as heparin-quaternary ammonium complexes may be incorporated into the hydrogel systems. Antimicrobial agents such as various silver compounds, quaternary ammonium compounds such as benzalkonium chloride, phenol derivatives such as thymol, and

antibiotics such as gentamycin, norfloxacin, and rifamycin can be incorporated into the hydrogel system. The hydrogel coatings can also be used as reservoirs for targeted drug delivery. Materials such as DNA or anticancer agents such as merbarone or methotrexate can be incorporated.

The bioactive agents can be incorporated by dissolution or dispersion into the coating solution prior to coating, or by imbibing into coated layers. Dispersion of silver salts can be made by forming the salt in situ from soluble starting components or by dispersing insoluble components using methods known to those skilled in the art. Many of the organic agents can be dissolved directly into the coating liquid. Agents such as merbarone, free base forms of norfloxacin and gentamicin are directly soluble in the solvents of the invention. Other agents that are typically ionic and that are usually available in salt forms usually must be converted into organic salts in order to be soluble in the solvents of the invention. For instance, gentamicin sulfate can be converted into the lauryl sulfate salt which is readily soluble in the solvents of the invention. Sodium heparin is usually converted into a salt of a quaternary ammonium compound such as benzalkonium chloride which is readily soluble in the solvents of the invention. Sodium methotrexate can be converted into a salt of a quaternary compound such as benzalkonium chloride which is readily soluble with solvents of the invention. Other combinations that are suitable to accomplish the invention will occur to those skilled in the art.

The method of the invention is beneficial because the components can be varied to control lubricity, stability, swelling, flexibility, adhesion, and resistance to removal by wet abrasion. These characteristics of the coating can thus be adjusted for various substrates and applications. The method is also beneficial because the solutions of the invention have good shelf stability and remain substantially free of precipitate for periods in the range of months or years, so that various mixtures of the solutions for coatings may be prepared at one time and used to coat substrates later. Alternatively, the hydrophilic and hydrophobic stabilizing polymers, and other components may even be prepared in a single solution.

Substantially all of the polymers deposited from solutions onto the surface of the object being coated remain in the layer of the coating after the solvents are evaporated. The duration and temperature of the evaporating step may be selected to achieve stability of the coating layer and to achieve a bond between the surface being coated and the coating layer.

Preferably, in a multi-layer or multiply embodiment, the outer layer solution contains some amount of an "active" solvent, i.e., a cosolvent, for the outer layer ingredients as well as the inner layer ingredients. As such, the active solvent causes the outer layer solution to penetrate into the inner layer, and is believed to bring about a mixing at the molecular level of the components of both layers.

It is believed that such molecular mixing may only comprise physical mixing without chemical reaction(s). In any event, in a preferred embodiment, there is a high degree of intermolecular mingling between the hydrophilic polymer and the stabilizing polymer in the coating, and in particular in a multi-layer coating, at the interface between the inner and outer layers of the coating relative to the outer surface of the outer layer. In practice, the activity of the solvent mixture is adjusted so that the degree of penetration of the outer layer into the inner layer is in a useful range. For example, if the outer layer solvent mixture is too active

toward the inner layer, then too much penetration into the inner layer occurs, and the outer layer will not be sufficiently lubricious when wet. Conversely, if the outer layer solvent is too inactive toward the inner layer, then too little penetration of outer layer into the inner layer occurs, and the coating is too easily removed from the inner layer by wet abrasion.

In an embodiment of the present invention, the lubricious hydrophilic layer and/or stabilizing polymer and/or bioactive agent is applied directly onto a polymer surface, and an active solvent is used which is a cosolvent for both the plastic substrate polymer or polymer mixture or at least one or more of the polymers in cases of mixed polymer substrates, and for the coating polymer(s) in the coating layer. After drying, the top coat polymer(s) layer is left partially embedded in the polymer surface. As in the case of the two-layer system, the solvent used during the coating application can be too active such that the top coat penetrates into the polymer surface to such a degree that the coated layer behaves as though it has been highly cross-linked. This prevents the top coat from becoming sufficiently swollen and lubricious when wet by aqueous fluids. In the case of a bioactive agent, it may not be exposed sufficiently to provide a physiological effect. Solvent mixtures can also be too inactive so that the coating is not resistant enough to abrasion when wet and is too easily removed.

The active solvents which are useful in the present invention may be individual solvents or solvent mixtures containing two or more solvents. In the case of solvent mixtures, one or more of the solvents in the mixture may be active while other solvent(s) in the mixture may be inactive. In any event, the solvent or solvent mixture dissolves or at least disperses the hydrophilic coating polymer and/or bioactive agent. In cases where the active agent is dispersed but not dissolved, a point is reached where the active agent goes into solution before all of the solvent has left the coating. During the phase of drying where the active agent is in solution, the solvent has also penetrated the substrate polymer(s) of the polymer surface. Thus, intermolecular mingling may take place between the substrate polymer(s) and the hydrogel polymer(s).

Examples of active solvents useful in the present invention include butyrolactone, alcohols, dimethyl acetamide, and n-methyl-2-pyrrolidone. These solvents and others cause different degrees of swelling of the plastic substrate or inner layer, as the case may be.

When tested by subjective methods the hydrogel coatings of the invention, when wet, are more slippery than wet, greased glass, and, when dry, are no more slippery than dry glass. The coatings of the invention are resistant to removal by wet abrasion as determined by running water over the coatings and rubbing between tightly gripped fingers while wet. The inventive coatings have high adherence when dry, as determined by attaching adhesive tape, pulling the tape off with a vigorous action, and then wetting the coated substrate to determine whether the taped portion retained the lubricant coating. The inventive coatings remain adherent and coherent for extended periods when stored in water, and neither peel off, dissolve, nor dissociate.

Suitable combinations of substrates, polymers, and solvents will be apparent to skilled practitioners. Generally, increasing the ratio of stabilizing polymer to water soluble polymer increases wet rub resistance and reduces lubricity. At high ratios, the hydrogel is not lubricious, and the coating can even be made to be hydrophobic. At low ratios, the hydrogel swells more in water and is less resistant to wet rub-off. The hydrogel may become impermanent or wash off easily.

The interaction between the stabilizing polymer and the hydrophilic polymer and/or the bioactive agent may be controlled to promote molecular entanglement. For example, the choice of solvent plays an important role. If a solvent is selected that allows a hydrogel layer to penetrate into the substrate layer, molecular entanglement at the interface layer results. This leads to increased wet rub resistance and decreased lubricity. Such factors may be taken into account by those skilled in the art when practicing this invention.

Examples of substrates and stabilizing polymer formulations that are effective with them are listed below. Many other combinations will be apparent to a person of ordinary skill following the teachings of the invention.

polyurethane:	hydroxyl function acrylic polymer; acrylic dispersion polymer; styrene acrylic copolymer; epoxy plus polyamide
polyethylene:	carboxyl function and hydroxyl function acrylic polymers plus melamine plus epoxy
silicone:	carboxyl function acrylic polymer plus epoxy resin
polyvinyl-chloride:	hydroxyl function acrylic polymer; polyvinylbutyral plus phenolic resin
acetal:	ethylene vinyl acetate copolymer; polyvinyl acetate copolymer
glass:	ethylene acrylic acid copolymer plus melamine resin plus acrylic polymer plus hydroxyl function acrylic polymer
stainless steel	epoxy plus polyamide, ethylene acrylic acid copolymer; acrylic polymer with carboxyl function plus epoxy resin.

The following examples show how the invention can be used. All amounts are given in grams except as indicated.

EXAMPLE 1

Polyurethane tubing was dip coated in the following solution, and dried 45 minutes at 85° C.

PVP	0.289
Benzyl alcohol	1.563
Ethanol	2.801
Cyclohexanone	5.347
Acrylic polymer with hydroxyl function	0.050
Xylene	0.050

Results

The coating was tested for adhesion by cutting lines through it with a knife and then rubbing briskly across the cuts with a finger after the coating was immersed in water. No failure of adhesion (i.e., peel back) occurred after the wet rub test. Next, the coating dry adhesion was tested by pressing Universal Tape 83436 tape (United Stationers Supply, Co.) firmly onto the coating and peeling the tape off briskly. No coating should be removed by this test. This sample showed no adhesion failure on the tape test. This coating had good lubricity when wet.

EXAMPLE 2

Oxygen plasma treated polyethylene tubing was dip coated in the following solution, and dried 45 minutes at 85° C.

5% (w/w) ethylene acrylic acid copolymer in THF	15.0
Cyclohexanone	4.0
Hydroxyl function acrylic polymer	0.24
Melamine resin	0.06
80% (w/w) isocyanate polymer in THF	0.32
Trichloroacetic acid	0.20

After the oven drying process, the sample was dip coated in the following solution and dried 1 hour at 80° C.

THF	74.00
Xylene	0.25
Acrylic copolymer with carboxyl function	13.88
Epoxy resin	0.75
Aromatic 150 solvent	9.73
Butyl Cellosolve	1.39

Next, the sample was dip coated in the following hydrogel solution and dried 1 hour at 80° C.

Butyrolactone	1.80
Dimethylacetamide	1.20
Ethanol	8.75
PVP	0.25
THF	0.60
Xylene	0.05
Epoxy resin	0.10
Polyamide resin	0.05

Results

This coating showed good dry adhesion, good lubricity, and good wet rub resistance when tested as per Example 1.

EXAMPLE 3 (COMPARATIVE)

This example compares improved coatings of the invention to the PVP-cellulose ester coatings of U.S. PAT. No. 5,331,027, and shows that the inventive coatings yield superior adhesion. Samples of silicone tubing were treated with an oxygen plasma process. Next, they were dip coated in the following solution and dried 120 minutes at 80° C.

Acrylic copolymer with carboxyl function	5.0
Aromatic 150 solvent	3.5
Butyl cellosolve	0.5
THF	27.75
Epoxy resin	0.56
Xylene	0.19

Next, Sample A was dip coated with the same hydrogel solution that was used in Example 2. Sample B was dip coated in the following solution for comparison (an example of the PVP-cellulose ester preparation of U.S. Pat. No. 5,331,027) and dried 2 hours at 80° C.

PVP	31.74
Ethanol	462.01
Butyrolactone	103.75
Cyclohexanone	12.82
Nitrocellulose	0.008

Results

The two coated samples were tested as per Example 1. The Sample A coated with the same hydrogel as Example 2

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showed good wet and dry adhesion and wet peel resistance, and was lubricious. Under the same test conditions Sample B coated with the PVP-cellulose ester hydrogel solution failed the dry adhesion and wet peel tests, showing that the coatings of this invention are superior to the prior technology.

EXAMPLE 4

The following solution was dip coated on polyurethane tubing and dried for 45 minutes at 85° C.

Ethanol	1.88
Benzyl alcohol	3.36
Cyclohexanone	6.42
PVP	0.35
Xylene	0.10
Acrylic copolymer with hydroxyl function	0.10

Results

This sample had good wet lubricity, wet adhesion, wet rub resistance, and dry adhesion when tested as per Example 1.

EXAMPLE 5

The following solution was dip coated on polyurethane tubing and dried for 45 minutes at 85° C.

Ethanol	1.88
Benzyl alcohol	3.36
Cyclohexanone	6.42
PVP	0.35
Crosslinkable acrylic aqueous emulsion (46% solids)	0.20

Results

This sample had good wet and dry adhesion, good peel resistance, and was lubricious when tested as per Example 1.

EXAMPLE 6

A sample of PVC tubing was dip coated in the following solution and dried 45 minutes at 85° C.

Ethanol	1.88
Benzyl alcohol	3.36
Cyclohexanone	6.42
PVP	0.35
Xylene	0.10
Acrylic polymer with hydroxyl function	0.10

Results

This sample had good wet lubricity, wet adhesion, wet rub resistance, and dry adhesion when tested as per Example 1.

EXAMPLE 7

PVC tubing was dip coated in the following solution and dried for 30 minutes at 85° C.

Ethanol	1.88
Benzyl alcohol	3.36

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-continued

Cyclohexanone	6.42
PVP	0.49
Xylene	0.15
Acrylic polymer with hydroxyl function	0.15

Results

This sample had good wet and dry adhesion and wet peel/rub resistance to removal and was lubricious when tested as per Example 1.

EXAMPLE 8 (COMPARATIVE)

This example compares the coatings of this invention to the PVP-cellulose ester coatings of U.S. PAT. No. 5,331,027 and shows that the inventive coatings yield superior adhesion. Samples of Nitinol wire (nickel-titanium alloy) coated with an aliphatic polyurethane were coated with one or the other of the following solutions, and dried for 1 hour at 85° C.

Sample A. Inventive technology	
Ethanol	1.88
Benzyl alcohol	3.36
Cyclohexanone	6.42
PVP	0.49
Xylene	0.15
Acrylic polymer with hydroxyl function	0.15
Sample B. Prior art (i.e., 5,331,027)	
Ethanol	1.88
Benzyl alcohol	3.36
Cyclohexanone	6.42
PVP	0.35
Nitrocellulose solution 0.0625% in cyclohexanone	0.14

Results

Sample A according to the invention had good wet and dry adhesion, good lubricity and good wet rub resistance. Sample B had poor wet adhesion, and poor wet rub resistance (the entire coating wiped off easily when wet). This comparison demonstrated the superiority of this invention over the prior art.

EXAMPLE 9

The following solution was dip coated on an acetal surface, air dried for 10 minutes and oven dried for 30–60 minutes at 85° C.

Ethylene vinyl acetate copolymer	1.5
THF	10.8
Cyclohexanone	2.7

Next, the sample was coated with the following hydrogel solution and was air dried for 10 minutes and oven dried for 30–60 minutes at 85° C.

PVP	0.75
Ethanol	11.40
Benzyl alcohol	2.85

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Results

This sample was lubricious and resistant to wet rub off and had good wet and dry adhesion.

EXAMPLE 10

Example 9 was repeated except that the coating that was applied under the hydrogel consisted of the following:

Polyvinyl acetate	4.0
Ethanol	12.8
Benzyl alcohol	3.2

Results

This sample was lubricious and resistant to wet rub off, and had good wet and dry adhesion.

EXAMPLE 11

The following was brush coated on a glass slide and dried 30 minutes at 85° C.

Precoat-	5% (w/w) ethylene acrylic acid copolymer in THF	15.0
	Cyclohexanone	4.0
	Hydroxyl function acrylic polymer	0.24
	Melamine resin	0.06
	80% (w/w) isocyanate	0.32
	Trichloroacetic acid	0.20

Next, the following coating was applied and dried for 60 minutes at 85° C.

Basecoat-	30% (w/w) acrylic polymer in toluene	9.9
	Cyclohexanone	8.8
	Benzyl alcohol	4.8
	Polyurethane	0.86
	THF	7.74
	Hydroxyl function acrylic polymer	1.80
	Melamine resin	0.45
	Trichloroacetic acid	0.1
	Xylene	1.76
	Butanol	0.49

Next, the hydrogel of Example 9 was applied and oven dried at 85° C for 30–60 minutes.

Results

This sample had good adhesion and lubricity.

EXAMPLE 12

The following was coated on a polyurethane tube and dried 60 minutes at 85° C.

Ethanol	18.8
Benzyl alcohol	33.6
Cyclohexanone	64.2
PVP	3.5
Acrylic polymer with carboxyl function	1.11
Aromatic 150 solvent	0.78
Butyl cellosolve	0.11
THF	1.67
Epoxy resin	0.25
Xylene	0.08

Results

This sample was lubricious and resistant to wet abrasion and had good adhesion.

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EXAMPLE 13

The following solution was coated on polyurethane tubing and dried for 18 hours at 85° C.

Ethanol	1.8
Benzyl alcohol	3.36
Cyclohexanone	6.42
PVP	0.35
Styrene acrylic copolymer	0.20
Water	0.20

Results

This sample was lubricious and resistant to wet abrasion and had good adhesion.

EXAMPLE 14

A stainless steel wire was coated with the following precoat and was dried for 60 minutes at 85° C.

5% (w/w) ethylene acrylic acid copolymer in THF	15.0
Epoxy resin	0.17
Xylene	0.06
THF	0.23

Next, the sample was coated with the following solution and dried 1 hour at 85° C.

Epoxy resin	0.37
Polyamide resin	0.18
Xylene	0.20
THF	6.24
PVP-vinylacetate copolymer	0.25
Ethanol	0.25
Cyclohexanone	1.00
Tridodecylmethyl ammonium heparinate	0.10

This sample was not designed to be lubricious. It had good wet and dry adhesion.

EXAMPLE 15

The following solution was dip coated on polyurethane tubing and dried 60 minutes at 85° C.

Ethanol	1.88
Benzyl alcohol	3.36
Dimethylacetamide	4.00
Cyclohexanone	6.42
PVP	0.35
Merbarone (a non-ionic cancer agent)	0.07
Acrylic copolymer with hydroxyl function	0.15
Xylene	0.15

Results

This sample of a medicated coating had good wet and dry adhesion and was resistant to wet abrasion.

EXAMPLE 16

The following solutions were coated on 5 Fr. polyurethane tubing and dried for 20 minutes at 85° C.

Solution 16A

Toluene	4.00
Xylene	0.15
IPA	3.00
Hydroxyl function acrylic copolymer	0.15
Cyclohexanone	1.00
50% (w/w) solution of PVP/VA in ethanol	0.50
Benzalkonium heparinate	0.10

Solution 16B

Toluene	7.00
IPA	2.00
Cyclohexanone	2.00
50% (w/w) solution of PVP/VA in ethanol	0.50
Acrylic polymer with hydroxyl function	0.20
Xylene	0.20

Solution 16C

Gensolve 2004	7.0
Cyclohexanone	1.0
Tridocleclmethyl ammonium heparinate	0.20
50% (w/w) ethanolic solution of PVP/VA	0.50
Hydroxyl function acrylic copolymer	0.20
Xylene	0.20

Solutions 16A, 16B, and 16C were dip coated on polyurethane tubing and dried for 20 minutes at 85° C. Next, the samples were tested for anti-clotting activity according to the appended clotting assay.

Results

Plasma clotted in minutes when exposed to the uncoated polyurethane tubing. The plasma did not clot even after exposure overnight to any of the three coated samples of Example 16. This demonstrates the strong antithrombogenic activity of the coatings.

EXAMPLE 17

A stainless steel wire (0.025" diameter) was dip coated with the following solution, and dried 60 minutes at 85° C.

5% (w/w) polyethylene acrylic acid copolymer in THF	10.0
Epoxy resin	0.113
Xylene	0.038
THF	0.15
Cyclohexanone	2.0

Next, the wire was dip coated in the same heparin containing hydroxyl coating solution as in Example 16A, and dried 20 minutes at 85° C. Next, the coated samples were tested for anticlotting activity using the same methods that were used in Example 16.

Results

The plasma clotted in minutes when exposed to the uncoated stainless steel. The plasma that was exposed to the coated sample did not clot overnight, demonstrating the strong antithrombogenic activity of the coating.

EXAMPLE 18

The following solution was prepared.

Xylene	0.60
THF	34.52
Epoxy resin	0.90
Polyamide	0.48

-continued

DNA	5.00
PVP	3.10
Ethanol	22.05

Next, various antimicrobial agents were mixed with 8.0 gm of the above solution.

Gentamycin free base	0.08 - dissolved
Norfloxacin free base	0.08 - dissolved
Rifamycin SV	0.09 - dissolved
Silver Sulfadiazine	0.08 - dispersed

Each solution was coated in 5 Fr polyurethane tubing and dried 45 minutes at 85° C. Next, the coated samples were tested for antimicrobial activity by "zone of inhibition" testing vs E. epi. Two samples of each were tested.

Results:

Antimicrobial Agents	Zone of Inhibition (cm)
Gentamycin free base	1.9/2.0
Norfloxacin free base	2.5/2.5
Rifamycin SV	4.5/4.5
Silver Sulfadiazine	0.7/0.7

These results demonstrate how various antimicrobial agents can be incorporated into the coatings of the invention while exhibiting their strong antimicrobial activity. It is expected that other types of agents can be incorporated into the coatings and be able to exert their activity in the region of the surface coating. For instance, agents could be incorporated in the coatings to treat cancer or restenoses in patients.

EXAMPLE 19

Polyurethane tubing was coated with the following solution and dried 20 minutes at 85° C.

Gensolve 2004	7
Cyclohexanone	1
50% (w/w) ethanolic solution of PVP-vinylacetate copolymer	0.5
50% solution of hydroxyl function acrylic polymer in xylene	0.4
Stearyl dimethylbenzyl ammonium heparinate	0.2

The sample was tested in the clotting assay of Example 16. The plasma did not clot even after exposure overnight.

EXAMPLE 20 (COMPARATIVE)

The following solution was prepared.

Solution 20A

RS Nitrocellulose	25.2
Toluene	11.3
Butyl acetate	17.0
Ethyl acetate	34.8

-continued

Solution 20A	
Dibutylphthalate	6.6
Camphor	4.8
2-Hydroxy-4-Methyl-Benzophenone	0.3

Next, the following solutions were made. 20B is representative of the technology of U.S. Pat. No. 5,001,009.

Solution 20B

Solution 20A	31.9
Cyclohexanone	22.8
Benzyl alcohol	22.8
Ethyl acetate	17.8
Iron Blue RS dispersion (Penn color)	2.3
Brown Oxide dispersion (Penn color)	0.7
TiO ₂ dispersion (Penn color)	1.6

Solution 20C

This is representative of the invention.

THF	67.5
Polyurethane resin	2.5
Cyclohexanone	10.0
Polyvinylbutyral	3.6
Phenolic resin	2.8

Next, solutions 20B and 20C were brush coated on an untreated flat inert polyethylene surface and dried for 60 minutes at 85° C. The colorants are known not to affect flexibility or adhesion. The polyurethane is an optional ingredient in this type of coating that is not necessary to confer flexibility. After cooling to room temperature, the coatings were peeled off the inert plastic surface to evaluate flexibility without the muting effect of the substrate. Such a coating will adhere to most substrates adequately although plasma treatment as in Example 2 or a pre-coat may be appropriate for larger flat applications.

Results

The 20B sample (prior art technology) cracked and broke into small brittle pieces. The 20C sample (inventive technology) peeled off evenly and was very flexible. It could be bent over tightly on itself and did not crack or fracture. It remained as a continuous, rubbery film that could be stretched without breaking. Flexibility of the peeled coating without cracking is predictive of coherence and flexibility as applied to a substrate. Flexibility as opposed to cracking of a peeled coating is predictive of a decreased likelihood of coating failure especially on substrates of smaller diameter and those expected to be subjected to extensive flexing. This demonstrates superior flexibility of the instant invention technology over conventional coatings.

EXAMPLE 21 (COMPARATIVE)

The following solutions were made.

Solution 21A

Solution 20A	37.7
Cyclohexanone	19.5
Benzyl alcohol	10.6
10% (w/w) polyurethane resin solution in THF	19.0

-continued

50% (w/w) hydroxyl function acrylic polymer solution in Xylene/Butanol (78/22)	10.00
Trichloroacetic acid	0.1
7.5% (w/w) Iron Blue dispersion (Penn color)	1.0
32.0% (w/w) TiO ₂ dispersion (Penn color)	1.4
11% (w/w) Brown Oxide dispersion Penn color)	0.7

Solution 21B

THF	74.0
Xylene	0.25
Acrylic polymer with carboxyl function	13.88
Epoxy resin	0.75
Aromatic 150 solvent	9.73
Butyl cellosolve	1.39

The solutions were dip coated on separate samples of 0.020 inch stainless steel coil guide wires which dried for 60 minutes at 85 ° C. Both coated guidewire samples were tested by pulling them tightly around a ¼" mandril and inspecting them for cracks in the coatings.

Results

The wire sample coated with 21A solution (prior art technology) had cracks, and sections between the cracks were straight. The sample coated with the technology of this invention had no cracks, and had a smooth, continuous arc as it bent around the mandril. This demonstrates the greater flexibility of this technology, and shows how it improves the flexibility of substrates coated with it compared to the prior art, especially on thinner (i.e. <0.050" diameter) devices that are designed to be flexible and which must be capable of maneuvering around multiple, relatively tight bends during use.

EXAMPLE 22

The following solution was dip coated on PVC tubing and air dried for 60 seconds.

Solution 22A

Polyurethane resin	3.0
Methylethylketone	42.9
N-methyl-2-pyrrolidone	15.0
THF	32.6
Phenolic resin	5.1
Polyvinylbutyral resin	0.3
Butanol	1.1

Next, the sample was dip coated in the following solution and dried at 80° C for 1–2 hours.

PVP	4.0
Ethanol	34.5
Benzyl alcohol	30.0
Isopropanol	30.0
Polyethyleneglycol 400	1.5

This sample had good wet lubricity and good adhesion.

The embodiments illustrated and discussed in this specification are intended only to teach those skilled in the art the best way known to the inventors to make and use the invention. Nothing in this specification should be considered as limiting the scope of the present invention. Modifications and variations of the above-described embodiments of the invention are possible without departing from the invention,

as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.

What is claimed is:

1. A coating applied to a surface of a medical device, the coating comprising:

(a) a stabilizing polymer selected from the group consisting of polymers based on cross-linkable acrylic and methacrylic polymers crosslinked with a crosslinker, ethylene acrylic acid copolymers, styrene acrylic copolymers, polyvinyl acetals, ethylene vinyl acetate copolymer, polyvinyl acetate, epoxy resins, amino resins, phenolic resins, copolymers thereof, and combinations; and

(b) an active agent selected from the group consisting of a hydrophilic polymer selected to interact with the stabilizing polymer so as to produce a lubricious hydrogel, a bioactive agent, and a combination,

the active agent being entrapped in the stabilizing polymer such that the coating adheres to the surface when dry and when wet, and remains coherent without cracking upon flexing of the surface.

2. A coating according to claim 1, wherein the stabilizing polymer is cross-linkable and further comprising a crosslinker for the stabilizing polymer.

3. A coating according to claim 2, wherein the cross-linker is selected from the group consisting of epoxy resin, melamine resin, other amino resin, and phenolic resin.

4. A coating according to claim 1, in which the stabilizing polymer has at least one component selected from the group consisting of acrylic with carboxyl, hydroxyl, amide, and methylol functional groups.

5. A coating according to claim 1, in which the surface of the medical device comprises a material selected from the group consisting of stainless steel, nickel, gold, chrome, nickel titanium alloy, platinum, another metal, silicone, polyethylene, other polyolefins, polyamide, polyesters, other plastics, glass, polyurethane, acetal, and polyvinyl chloride.

6. A coating according to claim 1, wherein the medical device is selected from the group consisting of needles, guide wires, catheters, surgical instruments, equipment for endoscopy, wires, stents, angioplasty balloons, wound drains, wound dressings, arteriovenous shunts, gastroenteric tubes, urethral inserts, laparoscopic equipment, pellets, and implants.

7. A coating according to claim 1, in which the stabilizing polymer is a cross-linkable acrylic selected from the group consisting of methylmethacrylate, butylmethacrylate, isobutylmethacrylate, ethylmethacrylate, methylacrylate, ethylacrylate, acrylic acid, methacrylic acid, styrene methacrylate, and styrene acrylate, and copolymers thereof.

8. The coating of claim 1 wherein the bioactive agent is selected from the group consisting of a pharmaceutical agent, a salt, an osmotic agent, and an oligonucleotide.

9. The coating of claim 1 further comprising an additive selected from the group consisting of a surfactant, a colorant, and a plasticizer.

10. The coating according to claim 1, wherein the coating comprises inner and outer layers having different proportions of the stabilizing polymer and the active agent.

11. The coating according to claim 1, wherein the coating thickness is less than about 50 microns.

12. The coating according to claim 1, wherein the active agent is a hydrophilic polymer and the coating is a hydrogel.

13. The coating according to claim 1, wherein the active agent is a bioactive agent.

14. The coating according to claim 12, wherein the coating comprises a bioactive agent.

15. The coating according to claim 1, wherein the coating resists wet abrasion and remains coherent despite flexing when applied to stainless steel.

16. The coating according to claim 1, wherein the selection of stabilizing polymer is independent of whether the stabilizing polymer is present in the substrate.

17. A method for coating a medical device having an inert surface comprising:

applying to the surface a coating liquid comprising a stabilizing polymer selected from the group consisting of polymers based on cross-linkable acrylic and methacrylic polymers, ethylene acrylic acid copolymers, styrene acrylic copolymers, polyvinyl acetals, ethylene vinyl acetate copolymer, polyvinyl acetate, epoxy resins, amino resins, phenolic resins, copolymers thereof, and combinations; and

applying a coating liquid comprising an active agent selected from the group consisting of a hydrophilic polymer selected to interact with the stabilizing polymer so as to produce a lubricious hydrogel, and a bioactive agent, and a combination, and

drying to remove liquids such that the crosslinkable acrylic and methacrylic polymers become crosslinked, the active agent is entrapped by the stabilizing polymer and the coating adheres to the surface when dry and wet, and remains coherent despite flexing of the surface.

18. A method according to claim 17, in which a single coating liquid comprises both the stabilizing polymer and the active agent.

19. A method according to claim 17, in which the applying step comprises dipping, spraying, brushing, or wiping.

20. A method according to claim 17, further comprising pretreating the surface of the medical device by gas plasma or other ionizing treatment before the applying step.

21. A method according to claim 17, wherein the drying comprises heating the coating to at least about 50° C.

22. A method for coating a medical device comprising a surface polymer selected from the group consisting of polymers based on cross-linkable acrylics, amino resins, phenolic resins, epoxy resins, polyvinylacetals, ethylene vinyl acetate copolymer, polyvinylacetate, copolymers thereof, and combinations; the method comprising the steps of

(a) applying a coating liquid comprising a solvent capable of attacking the device surface, and an active agent selected from the group consisting of a hydrophilic polymer selected to interact with the surface polymer so as to produce a lubricious hydrogel, and a bioactive agent, and a combination, and

(b) drying the coating liquid such that the crosslinkable acrylics become crosslinked, the active agent is entrapped in the surface polymer and the coating adheres to the surface when dry and wet, and remains coherent despite flexing of the medical device.

23. A kit for applying a coating to a medical device, comprising:

a liquid comprising a stabilizing polymer selected from the group consisting of polymers based on cross-linkable acrylic and methacrylic polymers crosslinked with a crosslinker, ethylene acrylic acid copolymers, styrene acrylic copolymers, polyvinylacetals, ethylene vinyl acetate copolymer, polyvinylacetate, epoxy resins, amino resins, phenolic resins, copolymers thereof, and combinations; and

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a liquid comprising an active agent selected from the group consisting of a hydrophilic polymer selected to interact with the stabilizing polymer so as to produce a lubricious hydrogel, and a bioactive agent, and a combination,

the liquids being the same or separate, and the stabilizing polymer and the active agent being selected to produce on the medical device a coherent flexible coating that has wet and dry adhesion.

24. The kit of claim 23, wherein the liquids are separate.

25. The kit of claim 24, wherein the liquid comprising the active agent further comprises a stabilizing polymer.

26. The kit of claim 24, wherein the liquid comprising the stabilizing polymer further comprises an active agent.

27. The kit of claim 23, wherein the liquid or liquids comprise a solvent selected from the group consisting of water, xylene, tetrahydrofuran, cyclohexanone, ethanol, butyrolactone, butanol, trichloroacetic acid, benzyl alcohol, isobutyl acetate, methyl ethyl ketone, Aromatic 150, toluene, and butyl cellosolve.

28. The kit of claim 23, wherein the stabilizing polymer liquid is an aqueous cross linkable acrylic dispersion.

29. The kit of claim 23, comprising a liquid comprising a cross-linker for the stabilizing polymer.

30. A medical device comprising a coating according to claim 1.

31. A coating according to claim 1 wherein the stabilizing polymer is selected from the group consisting of cross-linkable acrylic and methacrylic polymers, ethylene acrylic acid copolymers, styrene acrylic copolymers, vinyl acetate polymers, vinyl acetate copolymers, vinyl acetal polymers, vinyl acetal copolymers, epoxy, melamine, other amino resins, phenolic polymers, copolymers thereof, and combinations.

32. The coating according to claim 1, consisting essentially of the stabilizing polymer and the active agent.

33. A medical device comprising a coating according to claim 1 having a combination of substrate coated with stabilizing polymer formulation selected from the group consisting of: (a) polyurethane coated with stabilizing polymer formulation selected from the group consisting of one or more of styrene acrylic copolymer, and epoxy plus polyamide; (b) polyethylene coated with stabilizing polymer formulation selected from the group consisting of one or more of carboxyl function and hydroxyl function acrylic polymers plus melamine plus epoxy; (c) silicone with carboxyl function acrylic polymer plus epoxy resin; (d) polyvinylchloride coated with polyvinylbutyral plus phenolic resin; (e) acetal coated with stabilizing polymer formulation selected from the group consisting of one or more of ethylene vinyl acetate copolymer and polyvinyl acetate copolymer; (f) glass coated with ethylene acrylic acid copolymer plus melamine resin plus acrylic polymer plus hydroxyl function acrylic polymer; and (g) stainless steel coated with stabilizing polymer formulation selected from the group consisting of one or more of epoxy plus

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polyamide/ethylene acrylic acid copolymer, and acrylic polymer with carboxyl function plus epoxy resin.

34. A coated medical device produced by the method of claim 17.

35. A coated medical device produced by applying a kit according to claim 23 to a surface of the device.

36. A coating applied to a surface of a medical device, the coating comprising:

(a) a stabilizing polymer selected from the group consisting of polymers based on cross-linkable acrylic and methacrylic polymers, ethylene acrylic acid copolymers, styrene acrylic copolymers, polyvinyl acetals, ethylene vinyl acetate copolymer, polyvinyl acetate, epoxy resins, amino resins, phenolic resins, copolymers thereof, and combinations; and

(b) an active agent selected from the group consisting of a hydrophilic polymer selected to interact with the stabilizing polymer so as to produce a lubricious hydrogel, a bioactive agent, and a combination,

the active agent being entrapped in the stabilizing polymer such that the coating adheres to the surface when dry and when wet, and remains coherent without cracking upon flexing of the surface.

37. A coating according to claim 36, in which the stabilizing polymer has at least one component selected from the group consisting of acrylic with carboxyl, hydroxyl, amide, or methylol functional groups.

38. A coating according to claim 36, in which the surface of the medical device comprises a material selected from the group consisting of stainless steel, nickel, gold, chrome, nickel titanium alloy, platinum, another metal, silicone, polyethylene, other polyolefins, polyamide, polyesters, other plastics, glass, polyurethane, acetal, and polyvinyl chloride.

39. A coating according to claim 36, wherein the medical device is selected from the group consisting of needles, guide wires, catheters, surgical instruments, equipment for endoscopy, wires, stents, angioplasty balloons, wound drains, wound dressings, arteriovenous shunts, gastroenteric tubes, urethral inserts, laparoscopic equipment, pellets, and implants.

40. A medical device comprising a coating according to claim 36 having a combination of substrate coated with stabilizing polymer formulation selected from the group consisting of: (a) polyurethane coated with stabilizing polymer formulation selected from the group consisting of one or more of hydroxyl function acrylic polymer, crosslinkable acrylic dispersion polymer, styrene acrylic copolymer, and epoxy plus polyamide; (b) polyethylene coated with stabilizing polymer formulation selected from the group consisting of one or more of carboxyl function and hydroxyl function acrylic polymers plus melamine plus epoxy; and (c) polyvinylchloride coated with stabilizing polymer selected from the group consisting of hydroxy function acrylic polymer and polyvinylbutyral plus phenolic resin.

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(54) Title: STENT COATINGS COMPRISING HYDROPHILIC ADDITIVES

(57) Abstract: A coating for implantable medical devices and a method for fabricating thereof are disclosed. The coating includes a mixture of a hydrophobic polymer and a polymeric hydrophilic additive, wherein the hydrophobic polymer and the hydrophilic additive form a physically entangled or interpenetrating system.



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5 STENT COATINGS COMPRISING HYDROPHILIC ADDITIVES

BACKGROUND1. Field of the Invention

10 This invention relates to implantable medical devices such as stents. More particularly, the invention relates to materials that can be used to coat stents.

2. Description of Related Art

15 In the field of medical technology, there is frequently a necessity to administer drugs locally. To provide an efficacious concentration to the treatment site, systemic administration of medication often produces adverse or toxic side effects for the patient. Local delivery is a preferred method of treatment in that smaller total levels of medication are administered in comparison to systemic dosages, but are concentrated at a specific site. For the treatment of vascular lesions, stents can be modified with a polymeric coating to provide local drug delivery capabilities.

20 Examples of polymers that can be used to coat stents or other implantable devices include hydrophobic polymers, for example, poly(meth)acrylates, such as poly(*n*-butyl methacrylate) (PBMA) and copolymers or terpolymers having units derived from *n*-butyl methacrylate (BMA). PBMA and BMA-based coatings can provide effective control of the rate of release of a drug from a stent. In addition, PBMA and BMA-based polymers are
25 biocompatible, have good adhesion to the underlying stent surface, are easily processable, and possess good physical and mechanical properties such as ability to withstand elongation, compression, and shear that the stent undergoes during crimping onto the catheter, delivery to the lesion site, and expansion.

The properties of PBMA and BMA-based stent coatings can be improved, however. For
30 example, permeability of such coatings can be too low, particularly for drugs having higher molecular weights, leading to potentially insufficient supply of the drug to the diseased site. An ability to better regulate the rate of release through the coatings is desired. The present invention provides such coatings.

35 BRIEF DESCRIPTION OF DRAWINGS

FIGs. 1-3 are optical micrographs of coatings according to various embodiments of the present invention.

5 FIG. 4 is a graph illustrating kinetics of in vitro release of a drug through one stent coating of the present invention.

SUMMARY

10 An implantable medical device comprising a coating is provided, the coating includes a mixture of at least one poly(meth)acrylate and at least one polyalkylene glycol, wherein the macromolecular chains of the poly(meth)acrylate and the polyalkylene glycol form a physically entangled or interpenetrating system. Examples of the poly(meth)acrylate include poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(*iso*-propyl methacrylate), poly(*n*-butyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(*n*-propyl acrylate), poly(*iso*-propyl acrylate), poly(*n*-butyl acrylate), poly(*iso*-butyl acrylate), and mixtures thereof. Examples of the polyalkylene glycol include poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol), poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly(tetramethylene glycol), and mixtures thereof.

20 An implantable medical device comprising a coating is provided, the coating includes a mixture of at least one hydrophobic polymer and at least one polymeric hydrophilic compound, wherein the macromolecular chains of the hydrophobic polymer and the hydrophilic compound form a physically entangled or interpenetrating system. The hydrophobic polymer can include poly(meth)acrylates, vinyl polymers, polyolefins, halogenated polymers, polymers having urethane groups, polybutyrals, nylon, silicones, polycarbonate, or polysulfone. The polymeric hydrophilic compound can include polyalkylene glycols, hyaluronic acid, chondroitin sulfate, chitosan, glucosaminoglycans, dextran, dextrin, dextran sulfate, cellulose acetate, carboxymethyl cellulose, hydroxyethyl cellulose, cellulosics, polypeptides, poly(2-hydroxyethyl methacrylate), polyacrylamide, polyacrylimide, poly(ethylene amine), poly(allyl amine),
25 poly(vinyl pyrrolidone), poly(vinyl alcohol), poly(acrylic acid), poly(methacrylic acid), acrylic acid copolymers, methacrylic acid copolymers, polyvinyl alkyl ethers, non-ionic tetrafunctional block-copolymer surfactants, gelatin, collagen, albumin, chitin, heparin, elastin, fibrin, and mixtures thereof.

30 A medical article comprising an implantable substrate and a coating is provided, the coating includes a bulk polymer, an additive polymer in less quantity in the coating than the bulk polymer, the additive polymer being entangled or interpenetrated with the bulk polymer, and a drug.

5 A method for fabricating a coating for an implantable medical device is provided, the method comprises forming a coating on the device, the coating including a mixture of at least one hydrophobic polymer and at least one polymeric hydrophilic compound, wherein the macromolecular chains of the hydrophobic polymer and the hydrophilic compound form a physically entangled or intertwined system.

10 DETAILED DESCRIPTION

A coating for an implantable medical device, such as a stent, can include an optional primer layer, a drug-polymer layer, and an optional topcoat layer. The drug-polymer layer can be applied directly onto at least a part of the stent surface to serve as a reservoir for an active
15 agent or a drug which is incorporated into the drug-polymer layer. An optional primer layer can be applied between the stent and the drug-polymer layer to improve the adhesion of the drug-polymer layer to the stent. An optional topcoat layer can be applied over at least a part of the drug-polymer layer to reduce the rate of release of the drug from the reservoir.

The topcoat layer, if used, is the outermost layer of the stent coating. If the topcoat layer
20 is not used, the drug-polymer layer is the outermost layer of the stent coating. The drug-polymer and/or topcoat layer of the stent coating can include at least one hydrophobic polymer. To regulate a rate of release of the drug from the drug-polymer layer the hydrophobic polymer(s) can be physically mixed or blended with at least one polymeric hydrophilic additive to form a polymer system where the macromolecular chains of the hydrophobic polymer and the
25 hydrophobic additive are physically entangled, miscible, and/or interpenetrating. This polymer system can be, in one embodiment, the outermost region or layer of the coating.

Hereinafter, the hydrophobic polymer is also referred to as "polymer," and polymeric hydrophilic additive is also referred to as "additive." The term "physically entangled" is defined hereinafter as a polymer/additive composition in which neither the polymer nor the additive
30 forms a separate phase domain having a size larger than about 100 nanometers, such as the size larger than about 200 nanometers, for example, larger than about 300 nanometers. The size of the domain is determined by the largest linear dimension of the domain particle, e.g., by the diameter of a particle in case the domain particles are spheres. The definition of "physically entangled" also includes a condition that once the polymer and the additive have become
35 physically entangled, they do not disentangle but remain physically entangled for the duration of the service of the coating or until the drug has been released from the coating.

The hydrophobic polymer and the hydrophobic additive are defined hereinafter as "miscible" if the thermogram of the polymer/additive mixture shows substantially no thermal

5 transitions attributable to either the essentially pure polymer or the essentially pure additive. The thermogram can be obtained by a standard method of thermal analysis known to those having ordinary skill in the art, for example, by the method of differential scanning calorimetry.

The term "interpenetrating" is defined as the polymer/additive system where the polymer and the additive form an interpenetrating polymer network (IPN). The definition of the IPN
10 used by the International Union of Pure and Applied Chemistry (IUPAC) is adopted herein. The IUPAC describes the IPN as a polymer comprising two or more networks which are at least partially interlaced on a molecular scale, to form both chemical and physical bonds between the networks. The networks of an IPN cannot be separated unless chemical bonds are broken. In other words, an IPN structure represents two or more polymer networks that are partially
15 chemically cross-linked and partially physically entangled.

To define the terms "hydrophobic" and "hydrophilic" for the purposes of the present invention, one of the two criteria can be used. According to one criterion, a component in the polymer/additive system (i.e., the polymer or the additive) can be classified by the value of the component's equilibrium water adsorption. Whichever component in the polymer/additive
20 system has the greater value of the equilibrium water adsorption at room temperature is considered hydrophilic and the other component is considered hydrophobic. If more than two components are used in the polymer/additive system, then each can be ranked in order of its equilibrium water adsorption value. In one embodiment, the polymer is considered hydrophobic if it has an equilibrium water adsorption less than 10 mass % at room temperature, and the
25 additive is considered hydrophilic if it has an equilibrium water adsorption at room temperature of 10 mass % or greater.

According to another criterion, a component in the polymer/additive system can be classified by the value of the component's Hildebrand solubility parameter δ . The term

"Hildebrand solubility parameter" refers to a parameter measuring the cohesion of a
30 substance and is determined as follows:

$$\delta = (\Delta E/V)^{1/2}$$

where δ is the solubility parameter, $(\text{cal}/\text{cm}^3)^{1/2}$;

ΔE is the energy of vaporization, cal/mole; and

V is the molar volume, cm^3/mole .

35 Whichever component in the polymer/additive system has lower δ value compared to the δ value of the other component in the blend is designated as a hydrophobic component, and the other component with higher δ value is designated as hydrophilic. If more than two components are used in the blend, then each can be ranked in order of its δ value. In one exemplary

embodiment, the δ value defining the boundary between the hydrophobic and hydrophilic components of the polymer/additive system can be about $10.7 \text{ (cal/cm}^3)^{1/2}$.

Hydrophobic substances typically have a low δ value. In one embodiment, a component in the polymer/additive system that is "hydrophobic" can have a Hildebrand solubility parameter lower than about $10.7 \text{ (cal/cm}^3)^{1/2}$. A component in the polymer/additive system that is

"hydrophilic" can have a solubility parameter greater than about $10.7 \text{ (cal/cm}^3)^{1/2}$.

To make the polymer/additive mixture, the polymer can be blended with the additive and the blend can be dissolved in a solvent or in a system comprising a mixture of solvents. The term "dissolved" means that the polymer/additive blend, when combined with a suitable solvent or a mixture of solvents, is capable of forming a system which can be applied on a stent by a common technique, such as spraying or dipping. The solvent or a mixture of solvents can be selected by those having ordinary skill in the art depending, among other factors, on the nature of the polymer and the additive.

The polymer/additive solution can be then applied on the stent by a commonly known technique known to those having ordinary skill in the art, for example, by spraying or dipping, followed by drying, for example, by baking. The polymer/additive solution can be used to form the topcoat layer and/or the drug-polymer layer of the stent coating.

The combined mass concentration of the polymer and the additive in the polymer/additive solution can be between about 1% and about 10%, for example, about 2%. A ratio between the hydrophobic polymer and the polymeric hydrophilic additive in the polymer/additive solution can be between about 99:1 and about 9:1, such as between about 74:1 and about 14:1, more narrowly between about 49:1 and about 19:1. For example, for a polymer/additive solution containing about 2 mass % of the hydrophobic polymer, the concentration of the polymeric hydrophilic additive can be between about 0.04 and about 0.1 mass % of the total mass of the solution.

The polymer/additive solution can be prepared by various alternative methods. For example, the hydrophobic polymer and the polymeric hydrophilic additive can be dissolved separately to obtain a hydrophobic polymer solution and a polymeric hydrophilic additive solution, followed by combining the two solutions to form the polymer/additive solution. Alternatively, the hydrophobic polymer can be dissolved first to form the hydrophobic polymer solution, followed by adding the polymeric hydrophilic additive to the hydrophobic polymer solution to form the polymer/additive solution. As another alternative, the additive can be dissolved first to form the additive solution followed by adding the polymer to form the polymer/additive solution.

5 Examples of hydrophobic polymers include poly(meth)acrylates. The term
“poly(meth)acrylates” refers to both polymethacrylates and polyacrylates. Examples of
poly(meth)acrylates that can be used include homo-and copolymers of butyl methacrylate, for
example PBMA, poly(vinylidene fluoride-co butyl methacrylate), or poly(methyl methacrylate-
co-butyl methacrylate). Representative examples of other hydrophobic polymers that can be
10 used in practice of the present invention include the following polymers and mixtures thereof:

(a) poly(meth)acrylates other than PBMA or BMA-based polymethacrylates, such as
poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(*iso*-
propyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl
acrylate), poly(ethyl acrylate), poly(*n*-propyl acrylate), poly(*iso*-propyl acrylate), poly(*n*-butyl
15 acrylate), and poly(*iso*-butyl acrylate);

(b) vinyl polymers such as poly(ethylene-co-vinyl alcohol), for example, poly(ethylene-
co-vinyl alcohol) having a molar content of ethylene-derived units of at least 44 %,
poly(ethylene-co-vinyl acetate), poly(vinyl acetate), polystyrene, poly(styrene-co-*iso*-butylene),
poly(styrene-co-ethylene-co-butylene-co-styrene) terpolymers, and poly(styrene-co-butadiene-
20 co-styrene) terpolymers;

(c) polyolefins, for example, atactic polypropylene;

(d) halogenanated (e.g., fluorinated or chlorinated) polymers such as poly(vinyl fluoride),
poly(vinylidene fluoride), polyhexafluoropropene, poly(hexafluoropropene-co-vinylidene
fluoride), poly(ethylene-co-hexafluoropropene), various grades of amorphous TEFLON
25 (including polytetrafluoroethylene) available from E.I. Du Pont de Nemours & Co., poly(vinyl
chloride), and poly(vinylidene chloride);

(e) polymers having urethane groups, such as polyether urethanes, polyester urethanes,
polyurethaneureas, polycarbonate urethanes, and silicone urethanes; and

(f) polybutyrals, nylon, silicones, polycarbonate, and polysulfone.

30 Representative examples of polymeric hydrophilic additives that can be used in practice
of the present invention include hyaluronic acid, chondroitin sulfate, chitosan,
glucosaminoglucans, dextran, dextrin, dextran sulfate, cellulose acetate, carboxymethyl cellulose,
hydroxyethyl cellulose, cellulosics, poly(ethylene glycol)(PEG), poly(ethylene oxide),
poly(propylene glycol), PLURONIC, TETRONIC, poly(trimethylene glycol),
35 poly(tetramethylene glycol), polypeptides, poly(2-hydroxyethyl methacrylate), polyacrylamide,
polyacrylimide, poly(ethylene amine), poly(allyl amine), poly(vinyl pyrrolidone), poly(vinyl
alcohol), poly(acrylic acid), poly(methacrylic acid), acrylic acid copolymers, methacrylic acid
copolymers, polyvinyl alkyl ethers such as poly(vinylmethyl ether) or poly(vinylethyl ether);

5 gelatin, collagen, albumin, chitin, heparin, elastin, fibrin and mixtures thereof. PLURONIC is a trade name of a poly(ethylene oxide-co-propylene oxide). TETRONIC is a trade name of a family of non-ionic tetrafunctional block-copolymer surfactants. PLURONIC and TETRONIC are available from BASF Corp. of Parsippany, New Jersey.

10 To achieve the physical entanglement of the hydrophobic polymer and polymeric hydrophilic additive, at least one polymer and at least one additive can be blended together in a common solvent system that includes at least one very volatile solvent, followed by applying the solution onto a stent, for example, by spraying. As used herein, "very volatile solvent" means a solvent that has a vapor pressure greater than 30 Torr at ambient temperature. Examples of very volatile solvent include acetone and methyl ethyl ketone. Alternatively, to physically entangle
15 the hydrophobic polymer and polymeric hydrophilic additive, the polymer and the additive can be blended in the melt, and then applied to the stent from the melt, for example by curtain coating.

One way of forming an interpenetrating system of the hydrophobic polymer and polymeric hydrophilic additive is by blending the polymer and the additive in a solvent, or
20 solvent blend, in which both components are soluble. The solution can be applied onto a stent, for example, by spraying, followed by the removal of the solvent by drying. For the polymer and the additive which are capable of forming an interpenetrating system, the polymers and the additive are expected to interpenetrate while still in solution, and to remain interpenetrated upon solvent removal.

25 Alternatively, to form an interpenetrating system of the hydrophobic polymer and polymeric hydrophilic additive, the polymer and additive, which can be polymerized according to two different mechanisms, can be selected. For example, the hydrophobic component can be a carbonate urethane that is polymerized by condensation reactions between isocyanate and hydroxyl groups, while the hydrophilic additive can be poly(2-hydroxyethyl methacrylate) that
30 polymerizes by a free radical mechanism. The monomers may be dissolved in a common solvent system, applied to the stent, and then polymerized directly on the stent.

As another alternative way of forming an interpenetrating system of the hydrophobic polymer and polymeric hydrophilic additive, a high molecular weight polymer and additive can be selected, each component having reactive or associative groups that can interact with the
35 reactive or associative groups of the other component. For example, such hydrophilic additive as hydroxy terminated PEG can be blended with a high molecular weight, hydrophobic polyurethane with active isocyanate groups along the backbone. The additive and the polymer can be blended in solution, sprayed onto a stent, followed by curing. Although sometimes the

5 two components may be not miscible, the covalent bonds between them can still prevent phase separation.

To facilitate the formation of an entangled and/or interpenetrating hydrophobic polymer-polymeric hydrophilic additive system, the polymer and the additive can be selected in such a way that the chain lengths of the polymer and the additive, as determined by degree of
10 polymerization, are such as to promote the entanglement and/or interpenetration of the macromolecules of the polymer and the additive. The term "degree of polymerization" refers to a number of repeating monomeric units in a single macromolecule. The chain lengths that promote the formation of an entangled and/or interpenetrating network can be such that the contour length of the hydrophilic additive lies in the range of between about 10% and about
15 100% of the contour length of the hydrophobic polymer, for example, between 50% and 100%, such as 80%. The term "contour length" refers to the combined length of all bonds along the main chain (the backbone) of a macromolecule. The contour length can be approximated as the degree of polymerization multiplied by the number of bonds in the repeat unit. An average bond length of about 1.4 Å can be used for the computation. The following example can be used to
20 illustrate how the molecular weights of the polymer and the additive can be chosen to achieve a proper ratio between the contour lengths of the polymer and the additive.

PBMA with a number-averaged molecular weight (M_n) of about 200,000, has a degree of polymerization of 1,408 and has 2 bonds in the polymer backbone per repeat unit. Thus, a contour length of a PBMA macromolecule is about 3,940 Å. Suitable hydrophilic additive to
25 achieve entanglement can be PEG having contour lengths between about 394 Å and about 3,940 Å. PEG has 3 bonds per repeat unit, so for PEG having contour lengths between about 394 Å and about 3,940 Å, corresponding degree of polymerization is approximately between 131 and 1,313, and the corresponding M_n is between about 5,780 and about 57,800.

Generally, M_n of the hydrophobic polymer can be between about 50,000 and 1000,000
30 Daltons, for example, about 100,000 Daltons. The molecular weight of the hydrophilic additive can be between about 5,000 and about 100,000 Daltons, for example, about 40,000 Daltons. If PBMA is used as the hydrophobic polymer, the molecular weight of PBMA can be between about 100,000 and about 300,000 Daltons, for example, about 200,000 Daltons. If PEG is used as the hydrophilic additive being mixed with PBMA, the molecular weight of PEG can be
35 between about 10,000 and about 60,000 Daltons, for example, about 20,000 Daltons.

The embodiments of the present invention are described in connection with a stent, e.g., balloon expandable or self-expandable stents; however, other implantable medical devices can also be coated. Examples of such implantable devices include stent-grafts, grafts (e.g., aortic

5 grafts), artificial heart valves, cerebrospinal fluid shunts, pacemaker electrodes, and endocardial leads (e.g., FINELINE and ENDOTAK, available from Guidant Corp. of Santa Clara, California). The underlying structure of the device can be of virtually any design. The device can be made of a metallic material or an alloy such as, but not limited to, cobalt chromium alloy (ELGILOY), stainless steel (316L), "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, 10 nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from Standard Press Steel Co. of Jenkintown, Pennsylvania. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. Devices made from 15 bioabsorbable or biostable polymers could also be used with the embodiments of the present invention. The device itself can be made in whole or in part from the disclosed polymeric blends.

For the drug-polymer layer, the coating can include an active agent or a drug. The drug can include any substance capable of exerting a therapeutic or prophylactic effect for a patient. 20 The drug may include small molecule drugs, peptides, proteins, oligonucleotides, and the like. The drug could be designed, for example, to inhibit the activity of vascular smooth muscle cells. It can be directed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells to inhibit restenosis.

Examples of drugs include antiproliferative substances such as actinomycin D, or 25 derivatives and analogs thereof (manufactured by Sigma-Aldrich of Milwaukee, Wisconsin, or COSMEGEN available from Merck). Synonyms of actinomycin D include dactinomycin, actinomycin IV, actinomycin I₁, actinomycin X₁, and actinomycin C₁. The active agent can also fall under the genus of antineoplastic, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, antibiotic, antiallergic and antioxidant substances. Examples of such 30 antineoplastics and/or antimitotics include paclitaxel (e.g. TAXOL[®] by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g. Taxotere[®], from Aventis S.A., Frankfurt, Germany), methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g. Adriamycin[®] from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g. Mutamycin[®] from Bristol-Myers Squibb Co., Stamford, Conn.). Examples of such antiplatelets, anticoagulants, 35 antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and

5 thrombin inhibitors such as Angiomax™ (Biogen, Inc., Cambridge, Mass.). Examples of such
cytostatic or antiproliferative agents include angiopeptin, angiotensin converting enzyme
inhibitors such as captopril (e.g. Capoten® and Capozide® from Bristol-Myers Squibb Co.,
Stamford, Conn.), cilazapril or lisinopril (e.g. Prinivil® and Prinzide® from Merck & Co., Inc.,
Whitehouse Station, NJ); calcium channel blockers (such as nifedipine), colchicine, fibroblast
10 growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin
(an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name Mevacor® from
Merck & Co., Inc., Whitehouse Station, NJ), monoclonal antibodies (such as those specific for
Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors,
prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors,
15 triazolopyrimidine (a PDGF antagonist), and donors of nitric oxide. An example of an
antiallergic agent is permirrolast potassium. Other therapeutic substances or agents which may
be appropriate include alpha-interferon, genetically engineered epithelial cells, tacrolimus,
dexamethasone, and rapamycin and structural derivatives or functional analogs thereof, such as
40-O-(2-hydroxy)ethyl-rapamycin (known by the trade name of EVEROLIMUS available from
20 Novartis), 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin,
and 40-O-tetrazole-rapamycin.

The molecular weight of the drug can influence the choice of the molecular weights of
the polymer and the additive, as well as the ratios between the polymer and the additive, since
the release rate of the drugs having higher molecular weights is expected to be slower compared
25 with the release rate of the drugs with lower molecular weights. To illustrate, when the
PBMA/PEG topcoat system is used in conjunction with EVEROLIMUS (having molecular
weight 958 Daltons), M_n of PBMA can be between about 90,000 Daltons and about 300,000
Daltons, for example, about 190,000 Daltons and M_n of PEG can be between about 6,000
Daltons and about 20,000 Daltons, for example, about 18,000 Daltons, and the mass ratio
30 between PBMA and PEG can be between about 49:1 and about 9:1, for example, about 20:1. At
the same time, in the case of estradiol (having molecular weight of 272), M_n of PBMA can be
between about 150,000 Daltons and about 900,000 Daltons, for example, about 300,000 Daltons
and M_n of PEG can be between about 10,000 Daltons and about 50,000 Daltons, for example,
about 30,000 Daltons, and the mass ratio between PBMA and PEG can be between about 99 :1
35 and about 25:1, for example about 49:1.

Embodiments of the present invention are further illustrated by the following examples.

Example 1

A first polymer solution was prepared, the solution containing:

5 (a) about 5 mass % of poly(*n*-butyl methacrylate) (PBMA) having M_n of about 154,000; and

(b) the balance, solvent mixture of acetone and cyclohexanone, the mixture having a mass ratio between acetone and cyclohexanone of about 4:1.

A second polymer solution was prepared, the solution containing:

10 (a) about 5 mass % of poly(ethylene glycol) (PEG) having M_n of about 18,000; and
(b) the balance, solvent mixture of acetone and cyclohexanone, the mixture having a mass ratio between acetone and cyclohexanone of about 4:1.

The first polymer solution was combined with the second polymer solution to prepare a PBMA/PEG solution. The amount of the first and second polymer solutions were selected to
15 obtain the PBMA/PEG solution having a mass ratio between PBMA and PEG of about 49:1.

The PBMA/PEG solution was cast on a glass slide, and the solvent was removed by drying at room temperature followed by baking at about 80°C for about 1 hour. As a result, an adhered polymer film was formed on the glass slide. An optical micrograph of the dry PBMA/PEG film was taken in transmitted polarized light, as shown by FIG. 1. Under such
20 light, amorphous polymers appear dark and crystalline polymers appear bright. As seen from FIG. 1, the PBMA/PEG system appears uniformly dark showing good miscibility of PBMA and PEG. FIG. 1 does not show that PEG forms a separate phase.

Example 2

A PBMA/PEG solution was prepared as described in Example 1, except the mass ratio
25 between PBMA and PEG in the PBMA/PEG solution was about 19:1. A polymer film was formed on a glass slide out of the PBMA/PEG solution as described in Example 1. An optical micrograph of the dry PBMA/PEG film was taken as described in Example 1. The micrograph is shown by FIG. 2. As seen from FIG. 2, the PBMA/PEG system appears mostly uniform, with some amount of the crystalline phase formed by PEG represented by bright spots on the
30 micrograph.

Example 3

A PBMA/PEG solution was prepared as described in Example 1, except the mass ratio
between PBMA and PEG in the PBMA/PEG solution was about 10:1. A polymer film was formed on a glass slide out of the PBMA/PEG solution as described in Example 1. An optical
35 micrograph of the dry PBMA/PEG film was taken as described in Example 1. The micrograph is shown by FIG. 3. As seen from FIG. 3, the PBMA/PEG system includes visible crystalline areas. Compared with the film described in Example 2, the film shown by FIG. 3 included more substantial amount of the crystalline phase formed by PEG.

5

Example 4

A first composition was prepared by mixing the following components:

(a) between about 1.0 mass % and about 15 mass %, for example, about 2.0 mass % of poly(ethylene-co-vinyl alcohol) (EVAL); and

(b) the balance, DMAC solvent.

10

The first composition was applied onto the surface of a bare 18 mm VISION stent (available from Guidant Corp.) by spraying and dried to form a primer layer. A spray coater was used, having a 0.014 fan nozzle maintained at about 60°C with a feed pressure of about 0.2 atm (about 3 psi) and an atomization pressure of about 1.3 atm (about 20 psi). About 70 µg of the wet coating was applied. The wet coating was baked at about 140°C for about 2 hours, yielding a dry primer layer.

15

A second composition was prepared by mixing the following components:

(a) about 2.0 mass % of EVAL;

(b) about 1.6 mass % of EVEROLIMUS; and

(c) the balance, DMAC solvent.

20

The second composition was applied onto the dried primer layer to form a drug-polymer layer, using the same spraying technique and equipment used for applying the primer layer. About 300 µg of the wet coating was applied, followed by drying, e.g., by baking as described above. The dry drug-polymer layer contained about 130 µg of EVEROLIMUS.

A third composition was prepared by mixing the following components:

25

(a) about 2 mass % of PBMA having M_n of about 154,000; and

(b) about 0.1 mass % of PEG having M_n of about 18,000; and

(c) the balance, a 1:1 by mass mixture of solvents, acetone and cyclohexanone.

30

The third composition was applied onto the dried drug-polymer layer, to form a topcoat layer, using the same spraying technique and equipment used for applying the primer and the drug-polymer layers. About 200 µg of the wet coating was applied, followed by drying, e.g., by baking as described above. The final amount of the dried topcoat was about 50 µg.

The kinetics of release of EVEROLIMUS *in vitro* was studied chromatographically (HPLC). To study the kinetics, three stents were coated as described above in this Example.

The results of this study are illustrated by the chart shown by FIG. 4. The amount of

35

EVEROLIMUS released from a stent coating having the PBMA-PEG topcoat was measured (curve 1). The average of the data obtained from the three stents was used to plot curve 1. As a control, two identical control stents were used, except the topcoat included only pure PBMA instead of PBMA-PEG. The control curve 2 was plotted using the average of the data obtained

5 from the two control stents. As seen from FIG. 4, the rate of release of EVEROLIMUS through the PBMA-PEG topcoat is about twice the rate of release through the PBMA topcoat.

Example 5

A primer and drug-polymer layers can be formed on a stent as described in Example 4, but instead of EVEROLIMUS, rapamycin can be used. A topcoat composition can then be
10 prepared by mixing the following components:

- (a) about 2 mass % of PBMA having M_n of about 154,000; and
- (b) about 0.05 mass % of PEG having M_n of about 18,000;
- (c) about 0.05 mass % of poly(propylene glycol) (PPG) having M_n of about 40,000; and
- (c) the balance, a 1:1 by mass mixture of solvents, acetone and cyclohexanone.

15 If desired, poly(tetramethylene glycol) (PTMG) can be used in the topcoat composition instead of PPG. The M_n of PTMG can also be about 40,000. A PPG/PTMG blend having any ratio between PPG and PTMG can also be optionally used instead of PPG. In this example, in the topcoat composition the mass ratio between PEG and PPG is 1:1. If desired, the amount of PPG or PTMG, or a mixture thereof can be up to about twice amount of PEG. Optionally, all of
20 the PEG in the topcoat composition can be replaced with PPG or PTMG, or with a mixture thereof.

The topcoat composition can be applied onto the dried drug-polymer layer, to form a topcoat layer, using the same spraying technique and equipment used for applying the primer and the drug-polymer layers. About 200 μg of the wet coating can be applied, followed by
25 drying, e.g., by baking as described above. The final amount of the dried topcoat can be about 50 μg .

Example 6

A primer and drug-polymer layers can be formed on a stent as described in Example 4. A topcoat composition can then be prepared by mixing the following components:

- 30 (a) between about 1.0 mass % and about 15 mass %, for example, about 1.9 mass % of poly(hexafluoropropene-co-vinylidene fluoride) (PHFP-VDF) having M_n about 125,000.
- (b) between about 0.04 mass % and about 0.8 mass %, for example, about 0.1 mass % of F127 PLURONIC copolymer; and
- (c) the balance, a mixture of solvents, the solvent mixture including acetone and
35 cyclohexanone in a mass ratio of about 1:1.

F127 PLURONIC is a difunctional poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) triblock copolymer terminating in primary hydroxyl groups. F127 PLURONIC has M_n of about 12,600.

5 The topcoat composition can be applied onto the dried drug-polymer layer, to form a topcoat layer, using the same spraying technique and equipment used for applying the primer and the drug-polymer layers. About 200 μg of the wet coating can be applied, followed by drying, e.g., by baking as described above. The final amount of the dried topcoat can be about 50 μg .

10 While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

5 CLAIMS

WHAT IS CLAIMED IS:

1. An implantable medical device comprising a coating, the coating including a mixture of at least one poly(meth)acrylate and at least one polyalkylene glycol, wherein the macromolecular chains of the poly(meth)acrylate and the polyalkylene glycol form a physically
10 entangled or interpenetrating system.
2. The device of Claim 1, wherein the device is a stent.
3. The device of Claim 1, wherein a ratio between the poly(meth)acrylate and the polyalkylene glycol is between about 99:1 and about 9:1.
4. The device of Claim 1, wherein the poly(meth)acrylate is selected from a group
15 consisting of poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(*iso*-propyl methacrylate), poly(*n*-butyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(*n*-propyl acrylate), poly(*iso*-propyl acrylate), poly(*n*-butyl acrylate), poly(*iso*-butyl acrylate), and mixtures thereof.
- 20 5. The device of Claim 1, wherein the polyalkylene glycol is selected from a group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol), poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly(tetramethylene glycol), and mixtures thereof.
6. The device of Claim 1, wherein the coating additionally comprises a drug.
- 25 7. The device of Claim 6, wherein the drug is selected from a group consisting of rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, 40-O-tetrazole-rapamycin, and combinations thereof.
8. An implantable medical device comprising a coating, the coating including a mixture of at least one hydrophobic polymer and at least one polymeric hydrophilic compound,
30 wherein the macromolecular chains of the hydrophobic polymer and the hydrophilic compound form a physically entangled or interpenetrating system.
9. The device of Claim 8, wherein the device is a stent.
10. The device of Claim 8, wherein the hydrophobic polymer has a Hildebrand solubility parameter lower than about $10.7 \text{ (cal/cm}^3)^{1/2}$.
- 35 11. The device of Claim 8, wherein the hydrophobic polymer has an equilibrium water adsorption less than about 10 mass % at room temperature.

5 12. The device of Claim 8, wherein the hydrophobic polymer comprises poly(meth)acrylates, vinyl polymers, polyolefins, halogenanated polymers, polymers having urethane groups, polybutyrals, nylon, silicones, polycarbonate, or polysulfone.

10 13. The device of Claim 12, wherein the poly(meth)acrylates are selected from a group consisting of poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(*iso*-propyl methacrylate), poly(*n*-butyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(*n*-propyl acrylate), poly(*iso*-propyl acrylate), poly(*n*-butyl acrylate), poly(*iso*-butyl acrylate), and mixtures thereof.

15 14. The device of Claim 12, wherein the vinyl polymers are selected from a group consisting of poly(ethylene-co-vinyl alcohol), poly(ethylene-co-vinyl acetate), poly(vinyl acetate), polystyrene, poly(styrene-co-*iso*-butylene), poly(styrene-co-ethylene-co-butylene-co-styrene) terpolymers, and poly(styrene-co-butadiene-co-styrene) terpolymers, and mixtures thereof.

20 15. The device of Claim 12, wherein the polyolefin is atactic polypropylene.

 16. The device of Claim 12, wherein the halogenanated polymers are selected from a group consisting of poly(vinyl fluoride), poly(vinylidene fluoride), polyhexafluoropropene, poly(hexafluoropropene-co-vinylidene fluoride), poly(ethylene-co-hexafluoropropene), polytetrafluoroethylene, poly(vinyl chloride), poly(vinylidene chloride), and mixtures thereof.

25 17. The device of Claim 12, wherein the polymers having urethane groups are selected from a group consisting of polyether urethanes, polyester urethanes, polyurethaneureas, polycarbonate urethanes, silicone urethanes, and mixtures thereof.

30 18. The coating of Claim 8, wherein the polymeric hydrophilic compound is selected from a group consisting of polyalkylene glycols, hyaluronic acid, chondroitin sulfate, chitosan, glucosaminoglucans, dextran, dextrin, dextran sulfate, cellulose acetate, carboxymethyl cellulose, hydroxyethyl cellulose, cellulosics, polypeptides, poly(2-hydroxyethyl methacrylate), polyacrylamide, polyacrylimide, poly(ethylene amine), poly(allyl amine), poly(vinyl pyrrolidone), poly(vinyl alcohol), poly(acrylic acid), poly(methacrylic acid), acrylic acid copolymers, methacrylic acid copolymers, polyvinyl alkyl ethers, non-ionic tetrafunctional block-copolymer surfactants, gelatin, collagen, albumin, chitin, heparin, elastin, fibrin, and mixtures thereof.

35 19. The device of Claim 18, wherein the polyalkylene glycols are selected from a group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol),

5 poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly(tetramethylene glycol), and mixtures thereof.

20. The device of Claim 8, wherein the ratio between the hydrophobic polymer and the polymeric hydrophilic additive is between about 99:1 and about 9:1.

21. The device of Claim 8, wherein the coating additionally comprises a drug.

10 22. The device of Claim 21, wherein the drug is selected from a group consisting of rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, 40-O-tetrazole-rapamycin, and combinations thereof.

23. A medical article comprising an implantable substrate and a coating, the coating including:

15 (a) a bulk polymer;

(b) an additive polymer in less quantity in the coating than the bulk polymer, the additive polymer being entangled or interpenetrated with the bulk polymer; and

(c) a drug,

wherein the additive polymer changes the rate of release of the drug from the coating.

20 24. The medical article of Claim 23, wherein by increasing the ratio of the additive polymer to the bulk polymer, the rate of release of the drug is increased.

25. The medical article of Claim 23, wherein the bulk polymer is more hydrophobic than the additive polymer.

25 26. The medical article of Claim 23, wherein the bulk polymer includes a poly(meth)acrylate.

27. The medical article of Claim 23, wherein the poly(meth)acrylate is selected from a group consisting of poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(*iso*-propyl methacrylate), poly(*n*-butyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(*n*-propyl acrylate), poly(*iso*-propyl acrylate), poly(*n*-butyl acrylate), poly(*iso*-butyl acrylate), and mixtures thereof.

28. The medical article of Claim 23, wherein the additive polymer includes a polyalkylene glycol.

35 29. The medical article of Claim 28, wherein the polyalkylene glycol is selected from a group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol), poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly(tetramethylene glycol), and mixtures thereof.

5 30. The medical article of Claim 23, wherein the contour length of the additive polymer is between about 10% and about 100% of the contour length of the bulk polymer.

 31. A method of fabricating a coating for an implantable medical device, comprising forming a coating on the device, the coating including a mixture of at least one hydrophobic polymer and at least one polymeric hydrophilic compound, wherein the macromolecular chains
10 of the hydrophobic polymer and the hydrophilic compound form a physically entangled or intertwined system.

 32. The method of Claim 31, wherein the device is a stent.

 33. The method of Claim 31, wherein the hydrophobic polymer has a Hildebrand solubility parameter lower than about $10.7 \text{ (cal/cm}^3)^{1/2}$.

15 34. The method of Claim 31, wherein the hydrophobic polymer has an equilibrium water adsorption less than about 10 mass % at room temperature.

 35. The method of Claim 31, wherein the hydrophobic polymer comprises poly(meth)acrylates, vinyl polymers, polyolefins, halogenanated polymers, polymers having urethane groups, polybutyrals, nylon, silicones, polycarbonate, or polysulfone.

20 36. The method of Claim 35, wherein the poly(meth)acrylates are selected from a group consisting of poly(methyl methacrylate), poly(ethyl methacrylate), poly(*n*-propyl methacrylate), poly(*iso*-propyl methacrylate), poly(*n*-butyl methacrylate), poly(*iso*-butyl methacrylate), poly(*tert*-butyl methacrylate), poly(methyl acrylate), poly(ethyl acrylate), poly(*n*-propyl acrylate), poly(*iso*-propyl acrylate), poly(*n*-butyl acrylate), poly(*iso*-butyl acrylate), and
25 mixtures thereof.

 37. The method of Claim 35, wherein the vinyl polymers are selected from a group consisting of poly(ethylene-co-vinyl alcohol), poly(vinyl acetate), polystyrene, poly(styrene-co-*iso*-butylene), poly(styrene-co-ethylene-co-butylene-co-styrene) terpolymers, poly(styrene-co-butadiene-co-styrene) terpolymers, and mixtures thereof.

30 38. The method of Claim 35, wherein the polyolefin is atactic polypropylene.

 39. The method of Claim 35, wherein the halogenanated polymers are selected from a group consisting of poly(vinyl fluoride), poly(vinylidene fluoride), polyhexafluoropropene, poly(hexafluoropropene-co-vinylidene fluoride), poly(ethylene-co-hexafluoropropene), polytetrafluoroethylene, poly(vinyl chloride), poly(vinylidene chloride), and mixtures thereof.

35 40. The method of Claim 35, wherein the polymers having urethane groups are selected from a group consisting of polyether urethanes, polyester urethanes, polyurethaneureas, polycarbonate urethanes, silicone urethanes, and mixtures thereof.

5 41. The method of Claim 31, wherein the polymeric hydrophilic compound is selected from a group consisting of polyalkylene glycols, hyaluronic acid, chondroitin sulfate, chitosan, glucosaminoglucans, dextran, dextrin, dextran sulfate, cellulose acetate, carboxymethyl cellulose, hydroxyethyl cellulose, cellulotics, polypeptides, poly(2-hydroxyethyl methacrylate), polyacrylamide, polyacrylimide, poly(ethylene amine), poly(allyl amine),
10 poly(vinyl pyrrolidone), poly(vinyl alcohol), poly(acrylic acid), poly(methacrylic acid), acrylic acid copolymers, methacrylic acid copolymers, polyvinyl alkyl ethers, non-ionic tetrafunctional block-copolymer surfactants, gelatin, collagen, albumin, chitin, heparin, elastin, fibrin, and mixtures thereof.

15 42. The method of Claim 41, wherein the polyalkylene glycols are selected from a group consisting of poly(ethylene glycol), poly(ethylene oxide), poly(propylene glycol), poly(ethylene oxide-co-propylene oxide), poly(trimethylene glycol), poly(tetramethylene glycol), and mixtures thereof.

 43. The method of Claim 31, wherein a ratio between the hydrophobic polymer and the polymeric hydrophilic additive is between about 99:1 and about 9:1.

20 44. The method of Claim 31, wherein the coating additionally comprises a drug.

 45. The device of Claim 44, wherein the drug is selected from a group consisting of rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin, 40-O-tetrazole-rapamycin, and combinations thereof.

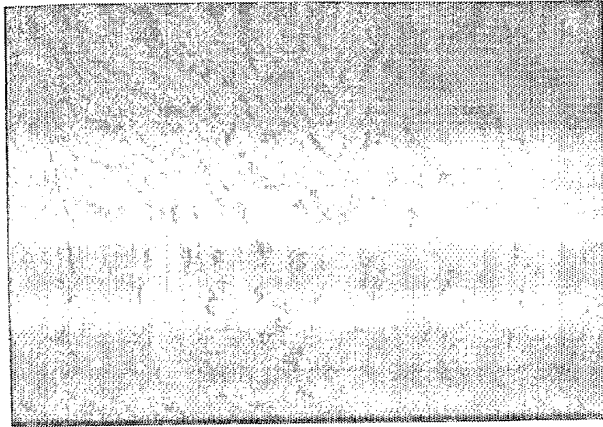


FIG. 1

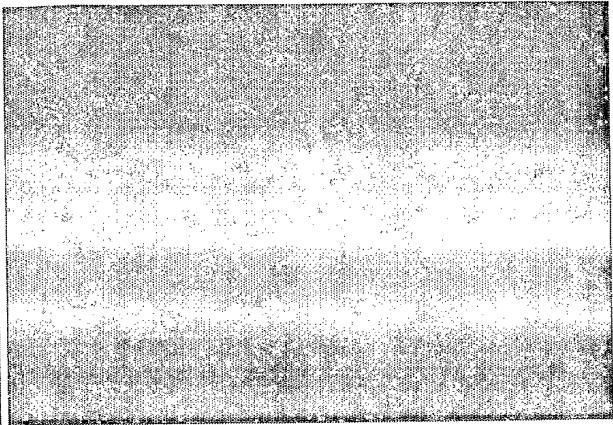


FIG. 2

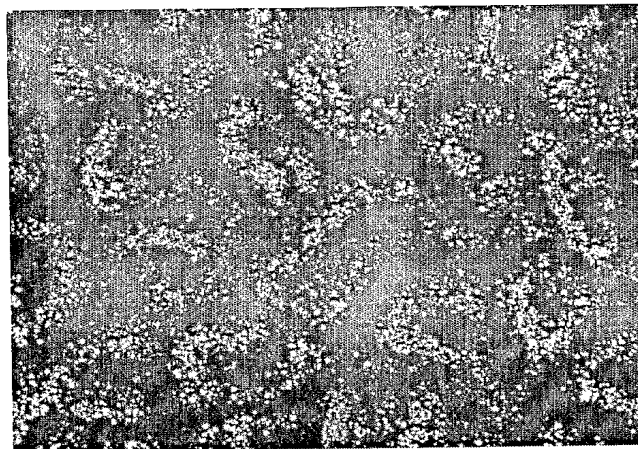


FIG. 3

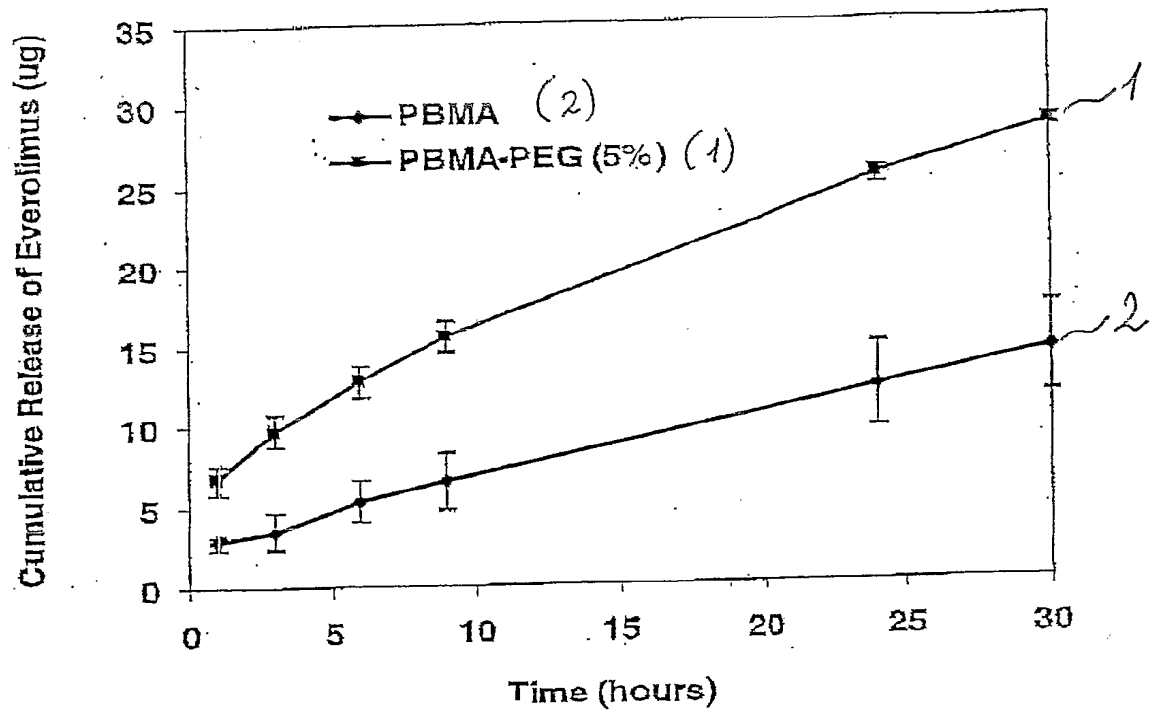


FIG. 4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/009011

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61L31/12 A61L31/10 A61L31/16 A61L27/34 A61L27/54
A61L27/40 A61L27/44 C08L33/10 C08L33/08 C08L71/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 120 904 A (DING NI ET AL) 19 September 2000 (2000-09-19) column 16, line 43 - line 65 column 17, line 17 - line 47 column 32, line 28 - line 36	8-12, 17-19, 31-35, 40-42
X	US 2002/133183 A1 (LENTZ DAVID CHRISTIAN ET AL) 19 September 2002 (2002-09-19) page 6, paragraph 69 page 7, paragraph 71 page 9, paragraph 87 page 18, paragraph 165 ----- -/--	8-12, 16, 18-27, 31-35, 39, 41-45

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

22 September 2004

Date of mailing of the international search report

05/10/2004

Name and mailing address of the ISA

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Authorized officer

Staber, B

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/009011

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 110 483 A (ZHANG XIANPING ET AL) 29 August 2000 (2000-08-29) column 2, line 13 - line 25 column 3, line 37 - line 42 column 3, line 45 - line 56 -----	8-14, 18-21, 23-29, 31-37, 41-44
P,X	WO 2004/010975 A (SCIMED LIFE SYSTEMS INC) 5 February 2004 (2004-02-05) page 6, paragraph 29 page 9, paragraph 38 page 10, paragraph 44 claims 2-5,7 -----	8-12,14, 18,19, 21,23, 31-35, 37,41, 42,44
X	US 590 263 A (BOSTON SCIENT LTD (BB)) 11 May 1999 (1999-05-11) column 4, line 47 - line 54 example 3 -----	1,2,5,6, 8,31
A	US 2002/065551 A1 (BINDERMAN ITZHAK ET AL) 30 May 2002 (2002-05-30) page 3, paragraph 34 page 3, paragraph 37 -----	1-45
P,A	WO 2004/009145 A (ADVANCED CARDIOVASCULAR SYSTEM) 29 January 2004 (2004-01-29) abstract -----	1-45

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US2004/009011

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/009011

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WO 2004009145	A	29-01-2004	WO	2004009145 A1	29-01-2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Examiner: Eric E. Silverman

HOSSAINY , Syed Faiyaz Ahmed

Serial No. 10/815,421

Art Unit: 1615

Filed: March 31, 2004

Confirmation No.: 7688

Customer number: 45159

Attorney Docket: 50623.359

Title: **BIOCOMPATIBLE POLYACRYLATE COMPOSITIONS FOR MEDICAL APPLICATIONS**

Mail Stop: **AMENDMENT**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT OF COMMON OWNERSHIP

Dear Sir:

At the time the invention of the current application (U.S. Serial Number 10/750,139) was made, the inventions of the current application and (WO 2004/101018 filed on March 24, 2004) were owned by, or subject to an obligation of assignment to, Advanced Cardiovascular Systems, Inc., a California corporation.

Date: January 9, 2008

Squire, Sanders & Dempsey L.L.P.
One Maritime Plaza, Suite 300
San Francisco, CA 94111
Telephone (415) 954-0200
Facsimile (415) 393-9887

Respectfully submitted,

/ZL/
Zhaoyang Li, Ph.D.
Attorney for Applicant
Reg. No. 46,872

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Examiner: Eric E. Silverman

Syed F.A. Hossainy

Serial No. 10/815,421

Art Unit: 1615

Filed: March 31, 2004

Confirmation No. 7688

Title: BIOCOMPATIBLE POLYACRYLATE COMPOSITIONS FOR MEDICAL APPLICATIONS

Mail Stop: **Amendment**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

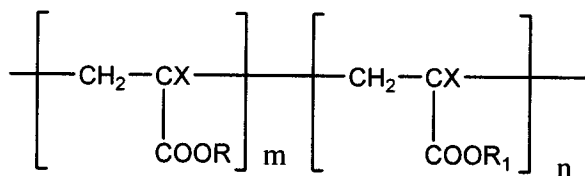
Amendment and Response to Office Action

Dear Examiner Silverman:

This response addresses the Office Action mailed on October 12, 2007.

In the Claims

1. (Withdrawn) A composition comprising:
 - (a) a biologically compatible structural component; and
 - (b) a biobeneficial component comprising a copolymer having a biobeneficial or bioactive moiety.
2. (Withdrawn) The composition of Claim 1 wherein the biologically compatible structural component comprises a linear acrylic homopolymer or a linear acrylic copolymer.
3. (Withdrawn) The composition of Claim 1 wherein the copolymer of the biobeneficial component additional has an acrylate moiety.
4. (Withdrawn) The composition of Claim 1 coated onto an implantable medical device.
5. (Withdrawn) The composition of Claim 1 wherein the mass ratio between the structural component and the biobeneficial component is between about 99:1 and about 1:1.
6. (Withdrawn) The composition of Claim 1 wherein the mass ratio between the structural component and the biobeneficial component is between about 19:1 and about 9:1.
7. (Withdrawn) The composition of Claim 1 wherein the mass ratio between the structural component and the biobeneficial component is about 3:1.
8. (Withdrawn) The composition of Claim 2 wherein the acrylic homopolymer or linear acrylic copolymer has the structure:



wherein

- (a) X is hydrogen or methyl group;
- (b) each of R and R₁ is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl;
- (c) m is a positive integer; and
- (d) n is 0 or a positive integer.

9. (Withdrawn) The composition of Claim 2 wherein the acrylic homopolymer or linear acrylic copolymer is poly(methylmethacrylate), poly(ethylmethacrylate), poly(n-propyl methacrylate), poly(iso-propylmethacrylate), poly(n-butylmethacrylate), poly(n-laurylmethacrylate), poly(2-hydroxyethylmethacrylate), poly(methylmethacrylate-co-2-hydroxyethyl methacrylate), poly(n-butylmethacrylate-co-2-hydroxyethyl methacrylate), or mixtures thereof.

10. (Withdrawn) The composition of Claim 1 wherein the biobeneficial component includes random, block, graft or brush copolymers.

11. (Withdrawn) The composition of Claim 10 wherein the block copolymers include AB-, ABA-, BAB-, ABC-, or ABCBA-block copolymers.

12. (Withdrawn) The composition of Claim 1 wherein the biobeneficial moiety includes fragments derived from poly(alkylene glycols), superoxide dismutate-mimetics (SODm),

diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

13. (Withdrawn) The composition of Claim 12 wherein the poly(alkylene glycols) are poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), poly(ethylene glycol-co-propylene glycol), poly(ethylene oxide-co-propylene oxide), or mixtures thereof.

14. (Withdrawn) The composition of Claim 12 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

15. (Withdrawn) The composition of Claim 12 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

16. (Withdrawn) The composition of Claim 15 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

17. (Withdrawn) The composition of Claim 16 wherein the heparin salts are sodium heparin, potassium heparin, lithium heparin, calcium heparin, magnesium heparin, adrenalin sodium, or mixtures thereof.

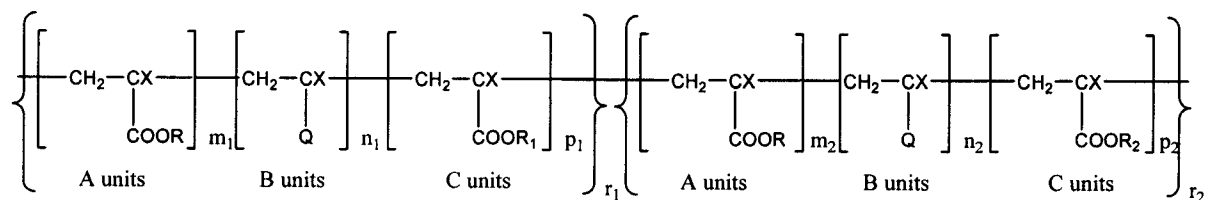
18. (Withdrawn) The composition of Claim 12 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

19. (Withdrawn) The composition of Claim 3 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 99:1 and about 1:1.

20. (Withdrawn) The composition of Claim 3 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 19:1 and about 9:1

21. (Withdrawn) The composition of Claim 3 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is about 3:1.

22. (Withdrawn) The composition of Claim 1 wherein the copolymer composing the biobeneficial component has the formula:



wherein

(a) $m_1, n_1, p_1, r_1, m_2, n_2, p_2,$ and r_2 are all integers;

(b) $m_1 \geq 0, n_1 > 0, p_1 \geq 0, r_1 > 0; m_2 \geq 0, n_2 > 0, p_2 \geq 0, r_2 > 0;$ and

(c)

(i) if $m_1 = 0$, then $p_1 > 0$;

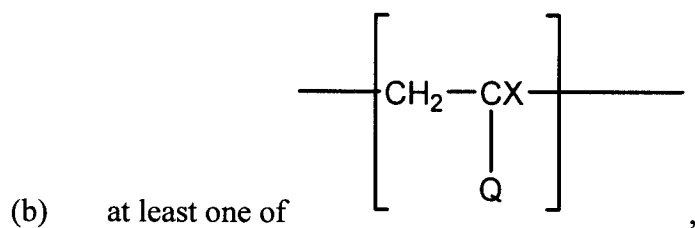
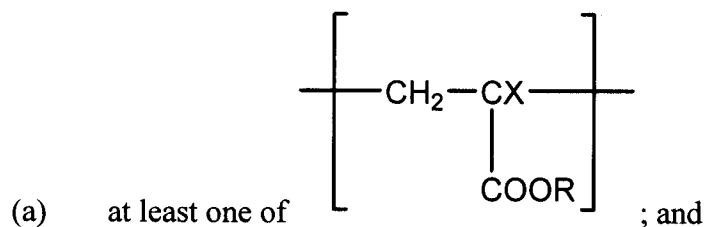
(ii) if $p_1 = 0$, then $m_1 > 0$; and

(iii) if $m_2 = 0$, then $p_2 > 0$; and

- (iv) if $p_2 = 0$, then $m_2 > 0$; and
 - (v) r_1 and r_2 are the same or different;
 - (vi) m_1 and m_2 are the same or different;
 - (vii) n_1 and n_2 are the same or different; and
 - (viii) p_1 and p_2 are the same or different;
- (d) X is hydrogen or methyl group;
- (e) each of R and R_1 , independently, is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (f) Q is a fragment providing the copolymer with biobeneficial or bioactive properties.

23. (Withdrawn) The composition of Claim 1 wherein the copolymer composing the biobeneficial component is poly(ethylene glycol)-block-poly(n-butylmethacrylate)-block-poly(ethylene glycol), poly(n-butylmethacrylate)-block-poly(ethylene glycol)-block-poly(n-butylmethacrylate), or mixtures thereof.

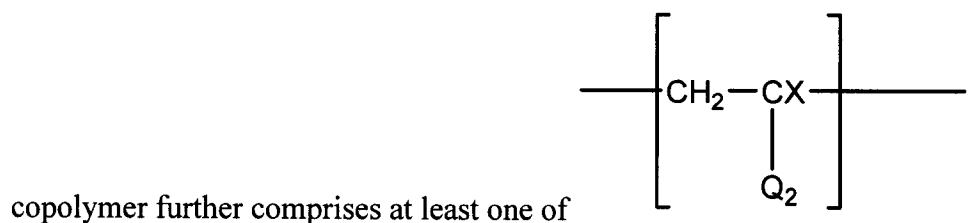
24. (Withdrawn) The composition of Claim 1 wherein the biobeneficial component includes a random, block, graft or brush copolymer comprising:



wherein

- (c) X is hydrogen or methyl group;
- (d) R is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (e) Q is a fragment providing the copolymer with biobeneficial properties.

25. (Withdrawn) The composition of Claim 24 wherein the biobeneficial component



wherein Q₂ is a fragment providing the copolymer with biobeneficial or bioactive properties provided that Q₂ is different from Q.

26. (Withdrawn) The composition of Claim 24 wherein Q is derived from poly(alkylene glycols), superoxide dismutase-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

27. (Withdrawn) The composition of Claim 26 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures of these.

28. (Withdrawn) The composition of Claim 26 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or blends thereof.

29. (Withdrawn) The composition of Claim 26 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

30. (Withdrawn) The composition of Claim 26 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

31. (Original) A medical article comprising an implantable medical device and a coating deposited on at least a part of the device, the coating including:

- (a) a structural component comprising a linear acrylic homopolymer or linear acrylic copolymer; and

- (b) a biobeneficial component comprising a copolymer having an acrylate moiety and a biobeneficial moiety.

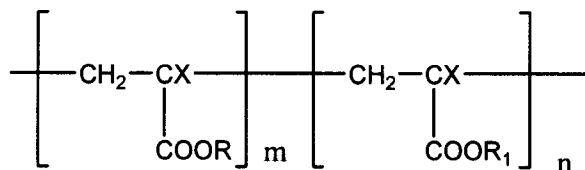
32. (Original) The medical article of Claim 31 wherein the implantable medical device is a stent.

33. (Original) The medical article of Claim 31 wherein the mass ratio between the structural component and the biobeneficial component is between about 99:1 and about 1:1.

34. (Original) The medical article of Claim 31 wherein the mass ratio between the structural component and the biobeneficial component is between about 19:1 and about 9:1.

35. (Original) The medical article of Claim 31 wherein the mass ratio between the structural component and the biobeneficial component is about 3:1.

36. (Original) The medical article of Claim 31 wherein the acrylic homopolymer and linear acrylic copolymer have the structure:



wherein

- (a) X is hydrogen or methyl group;
- (b) each of R and R₁ is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl;
- (c) m is a positive integer; and

(d) n is 0 or a positive integer.

37. (Original) The medical article of Claim 31 wherein the acrylic homopolymer or linear acrylic copolymer are poly(methylmethacrylate), poly(ethylmethacrylate), poly(n-propyl methacrylate), poly(iso-propylmethacrylate), poly(n-butylmethacrylate), poly(n-laurylmethacrylate), poly(2-hydroxyethylmethacrylate), poly(methylmethacrylate-co-2-hydroxyethyl methacrylate), poly(n-butylmethacrylate-co-2-hydroxyethyl methacrylate), or mixtures thereof.

38. (Original) The medical article of Claim 31 wherein the biobeneficial component includes random, block, graft or brush copolymers.

39. (Currently amended) The medical article of Claim 38 wherein the block copolymers include ~~AB, ABA, BAB, ABC, or ABCBA~~ AB, ABA, BAB, ABC, or ABCBA block copolymers.

40. (Currently amended) The medical article of Claim 31 wherein the biobeneficial moiety ~~is includes fragments derived~~ from poly(alkylene glycols), superoxide dismutate-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

41. (Original) The medical article of Claim 40 wherein the poly(alkylene glycols) are poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), poly(ethylene glycol-co-propylene glycol), poly(ethylene oxide-co-propylene oxide), or mixtures thereof.

42. (Withdrawn) The medical article of Claim 40 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -

guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

43. (Withdrawn) The medical article of Claim 40 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

44. (Withdrawn) The medical article of Claim 43 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

45. (Withdrawn) The medical article of Claim 44 wherein the heparin salts are sodium heparin, potassium heparin, lithium heparin, calcium heparin, magnesium heparin, ardeparin sodium, or mixtures thereof.

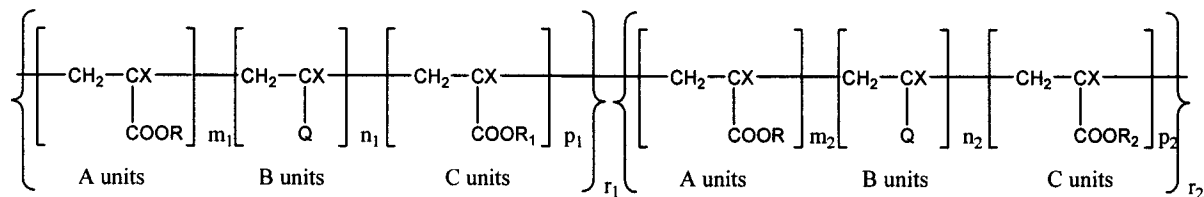
46. (Withdrawn) The medical article of Claim 40 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

47. (Original) The medical article of Claim 31 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 99:1 and about 1:1.

48. (Original) The medical article of Claim 31 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 19:1 and about 9:1

49. (Original) The medical article of Claim 31 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is about 3:1.

50. (Withdrawn) The medical article of Claim 31 wherein the copolymer composing the biobeneficial component has the formula:



wherein

(a) $m_1, n_1, p_1, r_1, m_2, n_2, p_2,$ and r_2 are all integers;

(b) $m_1 \geq 0, n_1 > 0, p_1 \geq 0, r_1 > 0; m_2 \geq 0, n_2 > 0, p_2 \geq 0, r_2 > 0;$ and

(c)

(i) if $m_1 = 0$, then $p_1 > 0$;

(ii) if $p_1 = 0$, then $m_1 > 0$; and

(iii) if $m_2 = 0$, then $p_2 > 0$; and

(iv) if $p_2 = 0$, then $m_2 > 0$; and

(v) r_1 and r_2 are the same or different;

(vi) m_1 and m_2 are the same or different;

(vii) n_1 and n_2 are the same or different; and

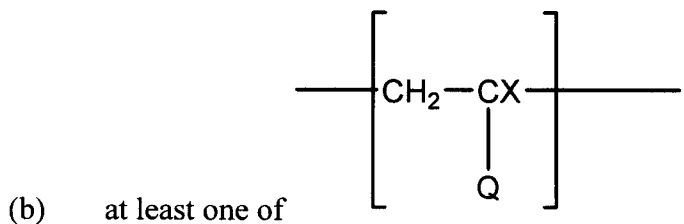
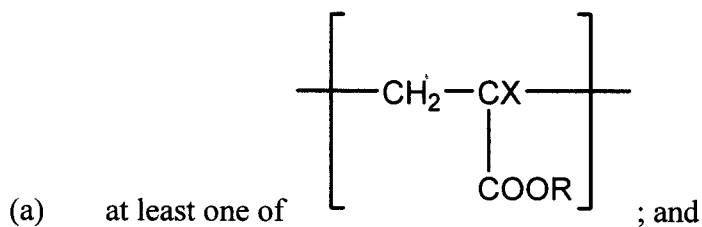
(viii) p_1 and p_2 are the same or different;

(d) X is hydrogen or methyl group;

- (e) each of R and R₁, independently, is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (f) Q is a fragment providing the copolymer with biobeneficial properties.

51. (Original) The medical article of Claim 31 wherein the copolymer composing the biobeneficial component is poly(ethylene glycol)-block-poly(n-butylmethacrylate)-block-poly(ethylene glycol), or poly(n-butylmethacrylate)-block-poly(ethylene glycol)-block-poly(n-butylmethacrylate).

52. (Original) The medical article of Claim 31 wherein the biobeneficial component includes a random, block, graft or brush copolymer composed of:



wherein

- (c) X is hydrogen or methyl group;
- (d) R is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and

- (e) Q is a fragment providing the copolymer with biobeneficial properties.

53. (Original) The composition of Claim 52 wherein Q is derived from poly(alkylene glycols), superoxide dismutase-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

54. (Original) The composition of Claim 53 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

55. (Original) The composition of Claim 53 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

56. (Original) The composition of Claim 53 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

57. (Original) The composition of Claim 53 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

58. (Withdrawn) A method for fabricating a medical article comprising depositing a polymeric blend comprising:

- (a) a biologically compatible structural component; and

- (b) a biobeneficial component comprising a copolymer having a biobeneficial or bioactive moiety.

on at least a portion of the implantable medical device to form a coating.

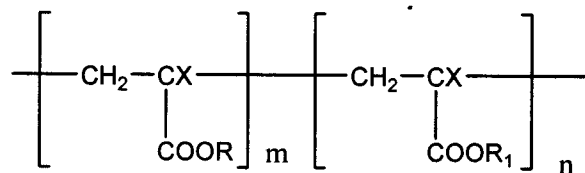
59. (Withdrawn) The method of Claim 58 wherein the implantable medical device is a stent.

60. (Withdrawn) The method of Claim 58 wherein the mass ratio between the structural component and the biobeneficial component is between about 99:1 and about 1:1.

61. (Withdrawn) The method of Claim 58 wherein the mass ratio between the structural component and the biobeneficial component is between about 19:1 and about 9:1.

62. (Withdrawn) The method of Claim 58 wherein the mass ratio between the structural component and the biobeneficial component is about 3:1.

63. (Withdrawn) The method of Claim 58 wherein the acrylic homopolymer or linear acrylic copolymer have the structure:



wherein

- (a) X is hydrogen or methyl group;
- (b) each of R and R₁ is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl;

(c) m is a positive integer; and

(d) n is 0 or a positive integer.

64. (Withdrawn) The method of Claim 58 wherein the acrylic homopolymer and linear acrylic copolymer are synthesized by polymerizing monomers selected from a group consisting of methylmethacrylate, ethylmethacrylate, n-propyl methacrylate, iso-propylmethacrylate, n-butylmethacrylate, n-laurylmethacrylate, 2-hydroxyethylmethacrylate, and mixtures thereof.

65. (Withdrawn) The method of Claim 58 wherein the step of preparing the polymeric blend includes synthesizing the biobeneficial random, block, graft or brush copolymers.

66. (Withdrawn) The method of Claim 65 wherein the block copolymers include AB-, ABA-, BAB-, ABC-, or ABCBA-block copolymers.

67. (Withdrawn) The method of Claim 65 wherein the step of synthesizing the block copolymers includes copolymerizing an acrylate and a biobeneficial monomer by a method of living, free-radical copolymerization with initiation-transfer agent termination of the living macro chains.

68. (Withdrawn) The method of Claim 67 wherein the acrylate is methylmethacrylate, ethylmethacrylate, n-propyl methacrylate, iso-propylmethacrylate, n-butylmethacrylate, n-laurylmethacrylate, 2-hydroxyethylmethacrylate, or mixtures thereof.

69. (Withdrawn) The method of Claim 67 wherein the biobeneficial monomer includes acryloyl-, methacryloyl-, vinyl, or allyl-modified adducts of superoxide dismutase-mimetics; acryloyl-, methacryloyl-, vinyl, or allyl-modified diazenium diolate type nitric oxide donors; or acryloyl-, methacryloyl-, vinyl, or allyl-modified polycationic peptides.

70. (Withdrawn) The method of Claim 67 wherein the biobeneficial monomer is 2-acrylamido-2-methyl-1-propanesulfonic acid, poly(ethylene glycol) methacrylate, 3-sulfopropyl acrylate, 3-sulfopropyl acrylate methacrylate, N-vinylpyrrolidone, vinyl sulfonic acid, 4-styrene sulfonic acid, or 3-allyloxy-2-hydroxypropanesulfonic acid.

71. (Withdrawn) The method of Claim 58 wherein the biobeneficial moiety includes fragments derived from poly(alkylene glycols), superoxide dismutate-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

72. (Withdrawn) The method of Claim 71 wherein the poly(alkylene glycols) are poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), poly(ethylene glycol-co-propylene glycol), poly(ethylene oxide-co-propylene oxide), or mixtures thereof.

73. (Withdrawn) The method of Claim 71 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

74. (Withdrawn) The method of Claim 71 wherein the polysaccharides are heparin, heparin derivatives, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

75. (Withdrawn) The method of Claim 74 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

76. (Withdrawn) The method of Claim 75 wherein the heparin salts are sodium heparin, potassium heparin, lithium heparin, calcium heparin, magnesium heparin, ardeparin sodium, or mixtures thereof.

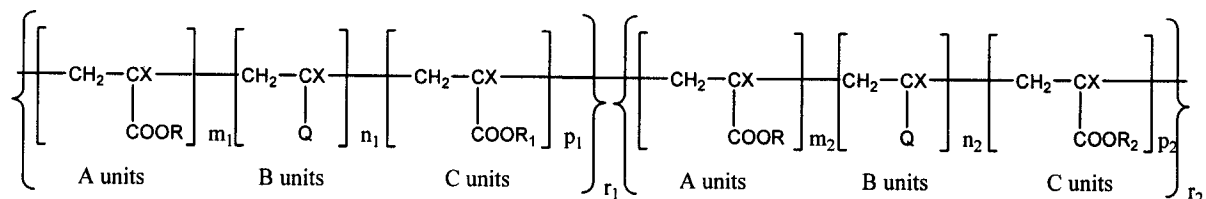
77. (Withdrawn) The method of Claim 71 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropane sulfonic acid, or mixtures thereof.

78. (Withdrawn) The method of Claim 58 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 99:1 and about 1:1.

79. (Withdrawn) The method of Claim 58 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 19:1 and about 9:1

80. (Withdrawn) The method of Claim 58 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is about 3:1.

81. (Withdrawn) The method of Claim 58 wherein the copolymer comprising the biobeneficial component has the formula:



wherein

(a) $m_1, n_1, p_1, r_1, m_2, n_2, p_2,$ and r_2 are all integers;

(b) $m_1 \geq 0, n_1 > 0, p_1 \geq 0, r_1 > 0; m_2 \geq 0, n_2 > 0, p_2 \geq 0, r_2 > 0;$ and

(c)

- (i) if $m_1 = 0$, then $p_1 > 0$;
- (ii) if $p_1 = 0$, then $m_1 > 0$; and
- (iii) if $m_2 = 0$, then $p_2 > 0$; and
- (iv) if $p_2 = 0$, then $m_2 > 0$; and
- (v) r_1 and r_2 are the same or different;
- (vi) m_1 and m_2 are the same or different;
- (vii) n_1 and n_2 are the same or different; and
- (viii) p_1 and p_2 are the same or different;

(d) X is hydrogen or methyl group;

(e) each of R and R_1 , independently, is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and

(f) Q is a fragment providing the copolymer with biobeneficial properties.

82. (Withdrawn) The method of Claim 58 wherein the copolymer comprising the biobeneficial component is poly(ethylene glycol)-block-poly(n-butylmethacrylate)-block-poly(ethylene glycol), poly(n-butylmethacrylate)-block-poly(ethylene glycol)-block-poly(n-butylmethacrylate), or mixtures thereof.

REMARKS

Claims 1-82 are pending. Claims 1-30, 42-46, 50, and 53-82 are withdrawn. Claims 31-41, 47-49, 51 and 52 are rejected.

Information Disclosure Statement

Applicants submitted two Information Disclosure Statements (IDSs) on October 6, 2004 and September 7, 2005, respectively. The Examiner signed off and returned the IDS filed on October 6, 2004 but has not returned to Applicants the signed off IDS filed on September 7, 2005. Applicants respectfully request the Examiner sign off the IDS filed on September 7, 2005 and return it to Applicants.

Rejections under 35 U.S.C. §112

Claims 39-41 are rejected as being indefinite under 35 U.S.C. §112, 2nd paragraph. Applicants believe these rejections are moot in light of the amendment to claims.

Rejections under 35 U.S.C. §103

Claims 31-41, 47-49, 51 and 52 are rejected as being obvious over U.S. Patent No. 6,110,483 to Whitbourne et al. ("Whitbourne") in view of WO 2004/101018 ("WO101018").

Claim 31 defines a medical article comprising an implantable medical device and a coating deposited on at least a part of the device. The coating includes (a) a structural component comprising a linear acrylic homopolymer or linear acrylic copolymer; and (b) a biobeneficial component **comprising a copolymer having an acrylate moiety and a biobeneficial moiety.**

Whitbourne describes a coating formed of poly(butyl methacrylate) (PBMA). As the Examiner correctly notes, Whitbourne fails to describe or teach a coating that includes a biobeneficial component **comprising a copolymer having an acrylate moiety and a biobeneficial moiety.**

WO 101018 describes a coating having a topcoat that includes PBMA and poly(ethylene glycol) (PEG), which can form an interpenetrating network. As the Examiner correctly notes, WO 101018 does not to describe or teach a coating that includes a biobeneficial component **comprising a copolymer having an acrylate moiety and a biobeneficial moiety.**

In addition, WO 101018 was filed on March 24, 2004, claiming priority to May 8, 2003. WO 101018 and the instant application were commonly owned by Advanced Cardiovascular Systems, Inc., when they were filed. WO 101018, even if it were relevant, would be a 103(a)/102(e) reference of the instant application and is disqualified as a prior art reference under 35 U.S.C. §103(c).

In sum, since WO 101018 is no longer a prior art reference and Whitbroune fails to describe or teach a coating that includes a biobeneficial component **comprising a copolymer having an acrylate moiety and a biobeneficial moiety**, claim 31 is patentably allowable over Whitbourne under 35 U.S.C. §103(a). Claims 32-41, 47-49, 51 and 52 depend from claim 31 and are patentably allowable over Whitbourne under 35 U.S.C. §103(a) for at least the same reason.

The undersigned authorizes the examiner to charge any fees that may be required or credit of any overpayment to be made to Deposit Account No. 07-1850.

CONCLUSION

Withdrawal of the rejection and allowance of the claims are respectfully requested. **If the Examiner has any suggestions or amendments to the claims to place the claims in condition for allowance, applicant would prefer a telephone call to the undersigned attorney for approval of an Examiner's amendment.** If the Examiner has any questions or concerns, the Examiner is invited to telephone the undersigned attorney at (415) 393-9885.

Date: January 9, 2008
Squire, Sanders & Dempsey L.L.P.
One Maritime Plaza, Suite 300
San Francisco, CA 94111
Telephone (415) 393-9885
Facsimile (415) 393-9887

Respectfully submitted,

/ZLI/
Zhaoyang Li, Ph.D., Esq.
Reg. No. 46,872

Electronic Acknowledgement Receipt

EFS ID:	2694926
Application Number:	10815421
International Application Number:	
Confirmation Number:	7688
Title of Invention:	Biocompatible polyacrylate compositions for medical applications
First Named Inventor/Applicant Name:	Syed F.A. Hossainy
Correspondence Address:	Cameron K. Kerrigan Squire, Sanders & Dempsey L.L.P. Suite 300 1 Maritime Plaza San Francisco CA 94111 US 4159540200 -
Filer:	Zhaoyang Li/LaRenda Meyer
Filer Authorized By:	Zhaoyang Li
Attorney Docket Number:	50623.359
Receipt Date:	09-JAN-2008
Filing Date:	31-MAR-2004
Time Stamp:	19:37:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment - After Non-Final Rejection	359.pdf	705394	no	23
			c53a5608f040819954d0333afeafd517be70e59f		

Warnings:

Information:

Total Files Size (in bytes):	705394
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875					Application or Docket Number 10/815,421		Filing Date 03/31/2004		<input type="checkbox"/> To be Mailed	
APPLICATION AS FILED – PART I										
(Column 1)			(Column 2)		SMALL ENTITY <input type="checkbox"/>		OR		OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)	RATE (\$)	FEE (\$)				
<input type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A		N/A					
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A		N/A					
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A		N/A					
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$	=	OR	X \$	=			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$	=		X \$	=			
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).									
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))										
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL				
APPLICATION AS AMENDED – PART II										
(Column 1)			(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY	
AMENDMENT	01/09/2008	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	RATE (\$)	ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))	* 82	Minus	** 82	= 0	X \$ =	OR	X \$50=	0	
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0	X \$ =	OR	X \$210=	0	
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))									
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE		TOTAL ADD'L FEE	0	
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$ =	OR	X \$ =		
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$ =	OR	X \$ =		
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))									
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE		TOTAL ADD'L FEE		
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.</p>										

Legal Instrument Examiner:
MARCIA J. GORDON

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.



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627/44SP1

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,421	03/31/2004	Syed F.A. Hossainy	50623.359	7688

7590

03/18/2008

Cameron K. Kerrigan
Squire, Sanders & Dempsey L.L.P.
Suite 300
1 Maritime Plaza
San Francisco, CA 94111

FINAL OFFICE ACTION
RESPONSE DUE: 6/18/08
APPEAL DUE: 2/18/08

EXAMINER

SILVERMAN, ERIC E

ART UNIT	PAPER NUMBER
----------	--------------

1618

MAIL DATE	DELIVERY MODE
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03/18/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DOCKETED: N/A

MAR 21 2008

BY AV AL
SQUIRE, SANDERS & DEMPSEY

Office Action Summary	Application No. 10/815,421	Applicant(s) HOSSAINY, SYED F.A.	
	Examiner Eric E. Silverman, PhD	Art Unit 1618	

- The MAILING DATE of this communication appears on the cover sheet with the correspondence address -
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 January 2008.
 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-82 is/are pending in the application.
 4a) Of the above claim(s) 1-30, 42-46, 50 and 53-82 is/are withdrawn from consideration.
 5) ☐ Claim(s) _____ is/are allowed.
 6) ☒ Claim(s) 31, 41, 47-49, 51, 52 is/are rejected.
 7) ☐ Claim(s) _____ is/are objected to.
 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date: _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' response, filed 1/9/2008, has been received.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 31 – 41, 47 - 49, 51 and 52 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,110,483 to Whitbourn in view of WO 2004/101018 for reasons of record and those discussed below.

Response to Arguments

Applicants' arguments have been fully considered, but are not persuasive. Applicants' first argue that the rejection of record agrees that the WO reference does not describe a coating including a biobeneficial agent comprising a copolymer having an acrylate and a biobeneficial moiety. This argument is not well understood. The Office Action mailed 10/12/2007 on pages 4 to 5 specifically notes that the WO reference teaches a PEG-PBMA-PEG, the elected biobeneficial component, which reads on this element as defined by applicant (applicant's definition of copolymer includes situations where the ends of the two polymers are not linked, and thus includes mixtures of homopolymers, as discussed on page 4 of the 10/12/2007 action). PBMA is polybutylmethacrylate, which has an acrylate moiety. Because the WO reference contains the elected species of obeneficial agent comprising a copolymer having an

acrylate and a biobeneficial moiety, it cannot be said that this reference does not teach this element.

Applicant also avers that the WO reference is barred as prior art under 35 U.S.C. 103(c). Specifically, Applicant alleges the following:

In addition, WO 101018 was filed on March 24, 2004, claiming priority to May 8, 2003. WO 101018 and the instant application were commonly owned by Advanced Cardiovascular Systems, Inc., when they were filed. WO 101018, even if it were relevant, would be a 103(a)/102(e) reference of the instant application and is disqualified as a prior art reference under 35 U.S.C. §103(c).

Applicants have misapplied section 103(c). The applicable part of that statute appears below.

(c)

(1) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Applicants stated that the prior art is competent only under 103(a) or 103(e). A more careful reading of the statute reveals that 103(c) does not apply to art that is competent under 102(a); it only applies to art that is competent only under one or more of 102(e), (f) and (g). As such Applicants' statement is not germane. Further Applicants stated that the WO reference and instant Application were commonly owned at the time of filing. A more careful reading of the statute reveals that 103(c) only applies to subject matter that was commonly owned at the time the invention was made. Again, Applicants' statement is not germane.

Because Applicants have presented nothing to show that the WO reference is excepted as prior art by 103(c), the argument that the WO reference cannot be applied is not persuasive.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric E. Silverman, PhD whose telephone number is (571)272-5549. The examiner can normally be reached on Monday to Thursday 7:00 am to 5:00 pm and Friday 7:00 am to noon.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571 272 0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Eric E. Silverman, PhD
Art Unit 1618

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Examiner: Eric E. Silverman

Syed F.A. Hossainy

Serial No. 10/815,421

Art Unit: 1615

Filed: March 31, 2004

Confirmation No. 7688

Title: BIOCOMPATIBLE POLYACRYLATE COMPOSITIONS FOR MEDICAL
APPLICATIONS

Mail Stop: **AF**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

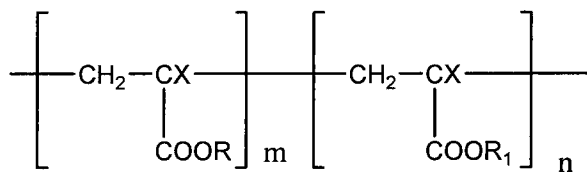
Amendment and Response to Final Office Action

Dear Examiner Silverman:

This response addresses the Final Office Action mailed on March 18, 2008.

In the Claims

1. (Withdrawn) A composition comprising:
 - (a) a biologically compatible structural component; and
 - (b) a biobeneficial component comprising a copolymer having a biobeneficial or bioactive moiety.
2. (Withdrawn) The composition of Claim 1 wherein the biologically compatible structural component comprises a linear acrylic homopolymer or a linear acrylic copolymer.
3. (Withdrawn) The composition of Claim 1 wherein the copolymer of the biobeneficial component additional has an acrylate moiety.
4. (Withdrawn) The composition of Claim 1 coated onto an implantable medical device.
5. (Withdrawn) The composition of Claim 1 wherein the mass ratio between the structural component and the biobeneficial component is between about 99:1 and about 1:1.
6. (Withdrawn) The composition of Claim 1 wherein the mass ratio between the structural component and the biobeneficial component is between about 19:1 and about 9:1.
7. (Withdrawn) The composition of Claim 1 wherein the mass ratio between the structural component and the biobeneficial component is about 3:1.
8. (Withdrawn) The composition of Claim 2 wherein the acrylic homopolymer or linear acrylic copolymer has the structure:



wherein

- (a) X is hydrogen or methyl group;
- (b) each of R and R₁ is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl;
- (c) m is a positive integer; and
- (d) n is 0 or a positive integer.

9. (Withdrawn) The composition of Claim 2 wherein the acrylic homopolymer or linear acrylic copolymer is poly(methylmethacrylate), poly(ethylmethacrylate), poly(n-propyl methacrylate), poly(iso-propylmethacrylate), poly(n-butylmethacrylate), poly(n-laurylmethacrylate), poly(2-hydroxyethylmethacrylate), poly(methylmethacrylate-co-2-hydroxyethyl methacrylate), poly(n-butylmethacrylate-co-2-hydroxyethyl methacrylate), or mixtures thereof.

10. (Withdrawn) The composition of Claim 1 wherein the biobeneficial component includes random, block, graft or brush copolymers.

11. (Withdrawn) The composition of Claim 10 wherein the block copolymers include AB-, ABA-, BAB-, ABC-, or ABCBA-block copolymers.

12. (Withdrawn) The composition of Claim 1 wherein the biobeneficial moiety includes fragments derived from poly(alkylene glycols), superoxide dismutate-mimetics (SODm),

diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

13. (Withdrawn) The composition of Claim 12 wherein the poly(alkylene glycols) are poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), poly(ethylene glycol-co-propylene glycol), poly(ethylene oxide-co-propylene oxide), or mixtures thereof.

14. (Withdrawn) The composition of Claim 12 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

15. (Withdrawn) The composition of Claim 12 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

16. (Withdrawn) The composition of Claim 15 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

17. (Withdrawn) The composition of Claim 16 wherein the heparin salts are sodium heparin, potassium heparin, lithium heparin, calcium heparin, magnesium heparin, adrenalin sodium, or mixtures thereof.

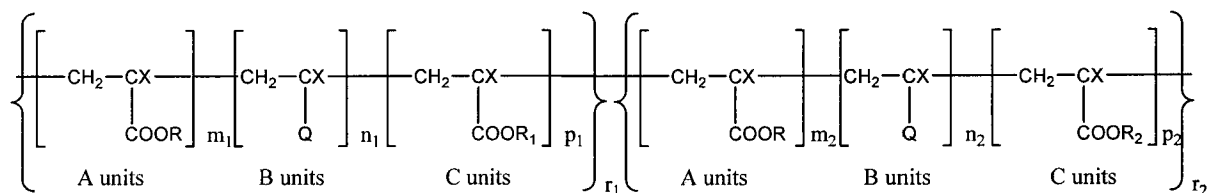
18. (Withdrawn) The composition of Claim 12 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

19. (Withdrawn) The composition of Claim 3 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 99:1 and about 1:1.

20. (Withdrawn) The composition of Claim 3 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 19:1 and about 9:1

21. (Withdrawn) The composition of Claim 3 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is about 3:1.

22. (Withdrawn) The composition of Claim 1 wherein the copolymer composing the biobeneficial component has the formula:



wherein

(a) $m_1, n_1, p_1, r_1, m_2, n_2, p_2,$ and r_2 are all integers;

(b) $m_1 \geq 0, n_1 > 0, p_1 \geq 0, r_1 > 0; m_2 \geq 0, n_2 > 0, p_2 \geq 0, r_2 > 0;$ and

(c)

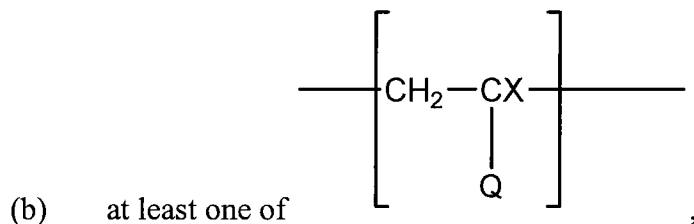
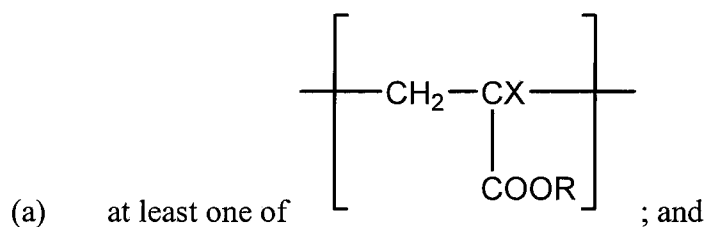
(i) if $m_1 = 0$, then $p_1 > 0$;

(ii) if $p_1 = 0$, then $m_1 > 0$; and

- (iii) if $m_2 = 0$, then $p_2 > 0$; and
 - (iv) if $p_2 = 0$, then $m_2 > 0$; and
 - (v) r_1 and r_2 are the same or different;
 - (vi) m_1 and m_2 are the same or different;
 - (vii) n_1 and n_2 are the same or different; and
 - (viii) p_1 and p_2 are the same or different;
- (d) X is hydrogen or methyl group;
- (e) each of R and R_1 , independently, is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (f) Q is a fragment providing the copolymer with biobeneficial or bioactive properties.

23. (Withdrawn) The composition of Claim 1 wherein the copolymer composing the biobeneficial component is poly(ethylene glycol)-block-poly(n-butylmethacrylate)-block-poly(ethylene glycol), poly(n-butylmethacrylate)-block-poly(ethylene glycol)-block-poly(n-butylmethacrylate), or mixtures thereof.

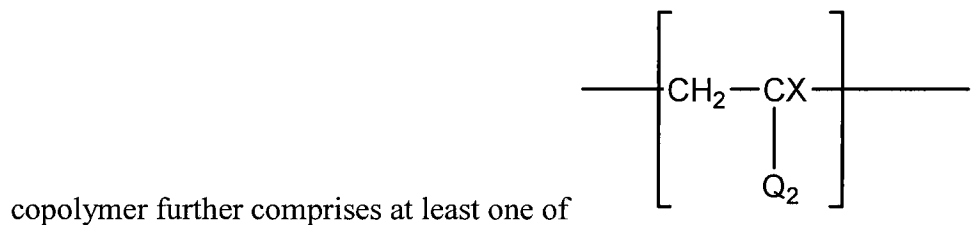
24. (Withdrawn) The composition of Claim 1 wherein the biobeneficial component includes a random, block, graft or brush copolymer comprising:



wherein

- (c) X is hydrogen or methyl group;
- (d) R is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (e) Q is a fragment providing the copolymer with biobeneficial properties.

25. (Withdrawn) The composition of Claim 24 wherein the biobeneficial component



wherein Q₂ is a fragment providing the copolymer with biobeneficial or bioactive properties provided that Q₂ is different from Q.

26. (Withdrawn) The composition of Claim 24 wherein Q is derived from poly(alkylene glycols), superoxide dismutate-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

27. (Withdrawn) The composition of Claim 26 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures of these.

28. (Withdrawn) The composition of Claim 26 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or blends thereof.

29. (Withdrawn) The composition of Claim 26 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

30. (Withdrawn) The composition of Claim 26 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

31. (Original) A medical article comprising an implantable medical device and a coating deposited on at least a part of the device, the coating including:

- (a) a structural component comprising a linear acrylic homopolymer or linear acrylic copolymer; and

- (b) a biobeneficial component comprising a copolymer having an acrylate moiety and a biobeneficial moiety.

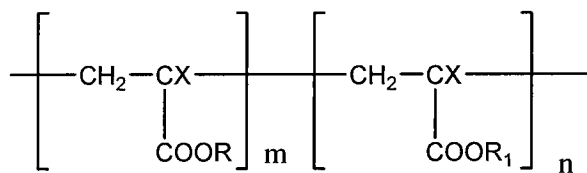
32. (Original) The medical article of Claim 31 wherein the implantable medical device is a stent.

33. (Original) The medical article of Claim 31 wherein the mass ratio between the structural component and the biobeneficial component is between about 99:1 and about 1:1.

34. (Original) The medical article of Claim 31 wherein the mass ratio between the structural component and the biobeneficial component is between about 19:1 and about 9:1.

35. (Original) The medical article of Claim 31 wherein the mass ratio between the structural component and the biobeneficial component is about 3:1.

36. (Original) The medical article of Claim 31 wherein the acrylic homopolymer and linear acrylic copolymer have the structure:



wherein

- (a) X is hydrogen or methyl group;
- (b) each of R and R₁ is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl;
- (c) m is a positive integer; and

(d) n is 0 or a positive integer.

37. (Original) The medical article of Claim 31 wherein the acrylic homopolymer or linear acrylic copolymer are poly(methylmethacrylate), poly(ethylmethacrylate), poly(n-propyl methacrylate), poly(iso-propylmethacrylate), poly(n-butylmethacrylate), poly(n-laurylmethacrylate), poly(2-hydroxyethylmethacrylate), poly(methylmethacrylate-co-2-hydroxyethyl methacrylate), poly(n-butylmethacrylate-co-2-hydroxyethyl methacrylate), or mixtures thereof.

38. (Original) The medical article of Claim 31 wherein the biobeneficial component includes random, block, graft or brush copolymers.

39. (Previously presented) The medical article of Claim 38 wherein the block copolymers include AB, ABA, BAB, ABC, or ABCBA block copolymers.

40. (Previously presented) The medical article of Claim 31 wherein the biobeneficial moiety is from poly(alkylene glycols), superoxide dismutate-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

41. (Original) The medical article of Claim 40 wherein the poly(alkylene glycols) are poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), poly(ethylene glycol-co-propylene glycol), poly(ethylene oxide-co-propylene oxide), or mixtures thereof.

42. (Withdrawn) The medical article of Claim 40 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

43. (Withdrawn) The medical article of Claim 40 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

44. (Withdrawn) The medical article of Claim 43 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

45. (Withdrawn) The medical article of Claim 44 wherein the heparin salts are sodium heparin, potassium heparin, lithium heparin, calcium heparin, magnesium heparin, ardeparin sodium, or mixtures thereof.

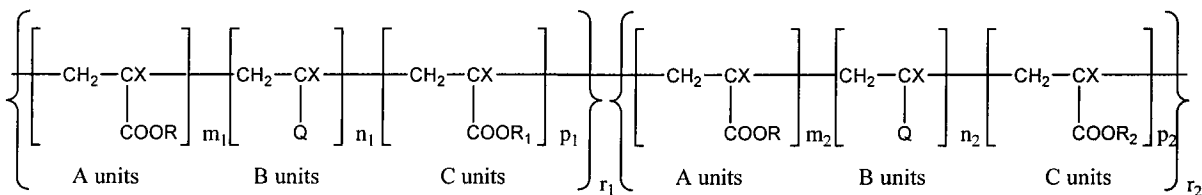
46. (Withdrawn) The medical article of Claim 40 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

47. (Original) The medical article of Claim 31 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 99:1 and about 1:1.

48. (Original) The medical article of Claim 31 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 19:1 and about 9:1

49. (Original) The medical article of Claim 31 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is about 3:1.

50. (Withdrawn) The medical article of Claim 31 wherein the copolymer composing the biobeneficial component has the formula:



wherein

(a) $m_1, n_1, p_1, r_1, m_2, n_2, p_2,$ and r_2 are all integers;

(b) $m_1 \geq 0, n_1 > 0, p_1 \geq 0, r_1 > 0; m_2 \geq 0, n_2 > 0, p_2 \geq 0, r_2 > 0;$ and

(c)

(i) if $m_1 = 0$, then $p_1 > 0$;

(ii) if $p_1 = 0$, then $m_1 > 0$; and

(iii) if $m_2 = 0$, then $p_2 > 0$; and

(iv) if $p_2 = 0$, then $m_2 > 0$; and

(v) r_1 and r_2 are the same or different;

(vi) m_1 and m_2 are the same or different;

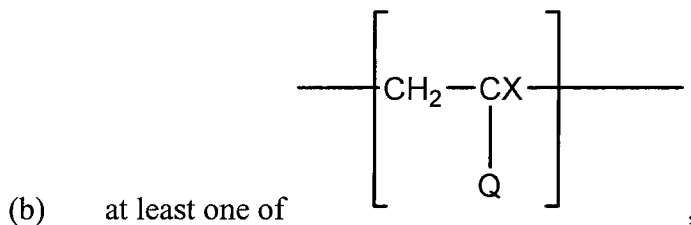
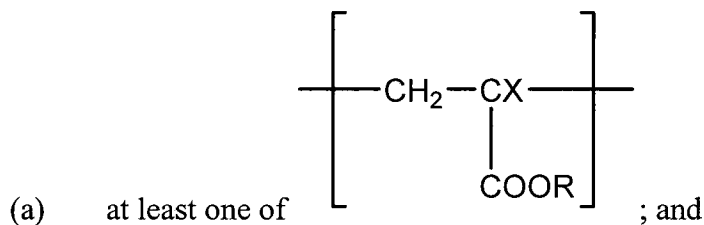
(vii) n_1 and n_2 are the same or different; and

(viii) p_1 and p_2 are the same or different;

- (d) X is hydrogen or methyl group;
- (e) each of R and R₁, independently, is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (f) Q is a fragment providing the copolymer with biobeneficial properties.

51. (Original) The medical article of Claim 31 wherein the copolymer composing the biobeneficial component is poly(ethylene glycol)-block-poly(n-butylmethacrylate)-block-poly(ethylene glycol), or poly(n-butylmethacrylate)-block-poly(ethylene glycol)-block-poly(n-butylmethacrylate).

52. (Original) The medical article of Claim 31 wherein the biobeneficial component includes a random, block, graft or brush copolymer composed of:



wherein

- (c) X is hydrogen or methyl group;

- (d) R is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and
- (e) Q is a fragment providing the copolymer with biobeneficial properties.

53. (Original) The composition of Claim 52 wherein Q is derived from poly(alkylene glycols), superoxide dismutase-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

54. (Original) The composition of Claim 53 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

55. (Original) The composition of Claim 53 wherein the polysaccharides are heparin or derivatives thereof, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

56. (Original) The composition of Claim 53 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

57. (Original) The composition of Claim 53 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropanesulfonic acid, or mixtures thereof.

58. (Withdrawn) A method for fabricating a medical article comprising depositing a polymeric blend comprising:

- (a) a biologically compatible structural component; and
- (b) a biobeneficial component comprising a copolymer having a biobeneficial or bioactive moiety.

on at least a portion of the implantable medical device to form a coating.

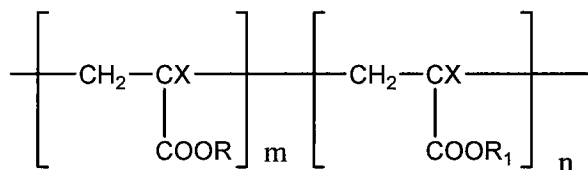
59. (Withdrawn) The method of Claim 58 wherein the implantable medical device is a stent.

60. (Withdrawn) The method of Claim 58 wherein the mass ratio between the structural component and the biobeneficial component is between about 99:1 and about 1:1.

61. (Withdrawn) The method of Claim 58 wherein the mass ratio between the structural component and the biobeneficial component is between about 19:1 and about 9:1.

62. (Withdrawn) The method of Claim 58 wherein the mass ratio between the structural component and the biobeneficial component is about 3:1.

63. (Withdrawn) The method of Claim 58 wherein the acrylic homopolymer or linear acrylic copolymer have the structure:



wherein

- (a) X is hydrogen or methyl group;

- (b) each of R and R₁ is independently methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl;
- (c) m is a positive integer; and
- (d) n is 0 or a positive integer.

64. (Withdrawn) The method of Claim 58 wherein the acrylic homopolymer and linear acrylic copolymer are synthesized by polymerizing monomers selected from a group consisting of methylmethacrylate, ethylmethacrylate, n-propyl methacrylate, iso-propylmethacrylate, n-butylmethacrylate, n-laurylmethacrylate, 2-hydroxyethylmethacrylate, and mixtures thereof.

65. (Withdrawn) The method of Claim 58 wherein the step of preparing the polymeric blend includes synthesizing the biobeneficial random, block, graft or brush copolymers.

66. (Withdrawn) The method of Claim 65 wherein the block copolymers include AB-, ABA-, BAB-, ABC-, or ABCBA-block copolymers.

67. (Withdrawn) The method of Claim 65 wherein the step of synthesizing the block copolymers includes copolymerizing an acrylate and a biobeneficial monomer by a method of living, free-radical copolymerization with initiation-transfer agent termination of the living macro chains.

68. (Withdrawn) The method of Claim 67 wherein the acrylate is methylmethacrylate, ethylmethacrylate, n-propyl methacrylate, iso-propylmethacrylate, n-butylmethacrylate, n-laurylmethacrylate, 2-hydroxyethylmethacrylate, or mixtures thereof.

69. (Withdrawn) The method of Claim 67 wherein the biobeneficial monomer includes acryloyl-, methacryloyl-, vinyl, or allyl-modified adducts of superoxide dismutate-mimetics;

acryloyl-, methacryloyl-, vinyl, or allyl-modified diazenium diolate type nitric oxide donors; or acryloyl-, methacryloyl-, vinyl, or allyl-modified polycationic peptides.

70. (Withdrawn) The method of Claim 67 wherein the biobeneficial monomer is 2-acrylamido-2-methyl-1-propanesulfonic acid, poly(ethylene glycol) methacrylate, 3-sulfopropyl acrylate, 3-sulfopropyl acrylate methacrylate, N-vinylpyrrolidone, vinyl sulfonic acid, 4-styrene sulfonic acid, or 3-allyloxy-2-hydroxypropanesulfonic acid.

71. (Withdrawn) The method of Claim 58 wherein the biobeneficial moiety includes fragments derived from poly(alkylene glycols), superoxide dismutate-mimetics (SODm), diazenium diolate type nitric oxide donors, polycationic peptides, polysaccharides, pyrrolidone, vitamin E, sulfonated dextrane, β -phenoxyethanol, N,N-dimethylamino-2-ethanol, mannose-6-phosphate, sulfonic acid, derivatives of sulfonic acid, or mixtures thereof.

72. (Withdrawn) The method of Claim 71 wherein the poly(alkylene glycols) are poly(ethylene glycol), poly(propylene glycol), poly(tetramethylene glycol), poly(ethylene glycol-co-propylene glycol), poly(ethylene oxide-co-propylene oxide), or mixtures thereof.

73. (Withdrawn) The method of Claim 71 wherein the polycationic peptides are poly(L-arginine), poly(D-arginine), poly(D,L-arginine), poly(L-lysine), poly(D-lysine), poly(δ -guanidino- α -aminobutyric acid), a racemic mixture of poly(L-arginine) or poly(D-arginine), or mixtures thereof.

74. (Withdrawn) The method of Claim 71 wherein the polysaccharides are heparin, heparin derivatives, glycosaminoglycans, keratan sulfate, chondroitin sulfate, dermatan sulfate, hyaluronic acid, hyaluronates, or mixtures thereof.

75. (Withdrawn) The method of Claim 74 wherein the derivatives of heparin are heparinoids, heparin having a hydrophobic counterion, heparan sulfate, heparin salts, or mixtures thereof.

76. (Withdrawn) The method of Claim 75 wherein the heparin salts are sodium heparin, potassium heparin, lithium heparin, calcium heparin, magnesium heparin, ardeparin sodium, or mixtures thereof.

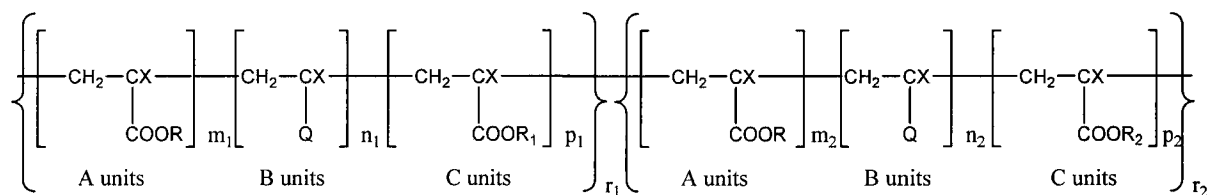
77. (Withdrawn) The method of Claim 71 wherein the derivatives of sulfonic acid are propanesulfonic acid, 2-methyl-1-propanesulfonic acid, benzenesulfonic acid, 3-methoxy-2-hydroxypropane sulfonic acid, or mixtures thereof.

78. (Withdrawn) The method of Claim 58 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 99:1 and about 1:1.

79. (Withdrawn) The method of Claim 58 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is between about 19:1 and about 9:1

80. (Withdrawn) The method of Claim 58 wherein the mass ratio between the acrylate moiety and the biobeneficial moiety is about 3:1.

81. (Withdrawn) The method of Claim 58 wherein the copolymer comprising the biobeneficial component has the formula:



wherein

(a) $m_1, n_1, p_1, r_1, m_2, n_2, p_2,$ and r_2 are all integers;

(b) $m_1 \geq 0, n_1 > 0, p_1 \geq 0, r_1 > 0; m_2 \geq 0, n_2 > 0, p_2 \geq 0, r_2 > 0;$ and

(c)

- (i) if $m_1 = 0$, then $p_1 > 0$;
- (ii) if $p_1 = 0$, then $m_1 > 0$; and
- (iii) if $m_2 = 0$, then $p_2 > 0$; and
- (iv) if $p_2 = 0$, then $m_2 > 0$; and
- (v) r_1 and r_2 are the same or different;
- (vi) m_1 and m_2 are the same or different;
- (vii) n_1 and n_2 are the same or different; and
- (viii) p_1 and p_2 are the same or different;

(d) X is hydrogen or methyl group;

(e) each of R and R_1 , independently, is methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, lauryl, or 2-hydroxyethyl; and

(f) Q is a fragment providing the copolymer with biobeneficial properties.

82. (Withdrawn) The method of Claim 58 wherein the copolymer comprising the biobeneficial component is poly(ethylene glycol)-block-poly(n-butylmethacrylate)-block-poly(ethylene glycol), poly(n-butylmethacrylate)-block-poly(ethylene glycol)-block-poly(n-butylmethacrylate), or mixtures thereof.

REMARKS

Claims 1-82 are pending. Claims 1-30, 42-46, 50, and 53-82 are withdrawn. Claims 31-41, 47-49, 51 and 52 are rejected.

Information Disclosure Statement

In the Response to Office Action submitted on January 9, 2008, Applicant pointed out that the Examiner signed off and returned the IDS filed on October 6, 2004 but has not returned to Applicant the signed off IDS filed on September 7, 2005. Applicant requested the Examiner sign off the IDS filed on September 7, 2005 and return it to Applicant. This Final Office Action is silent on the Applicant's request. For record, Applicant assumes all the references in the IDS filed on September 7, 2005 were considered.

Rejections under 35 U.S.C. §103

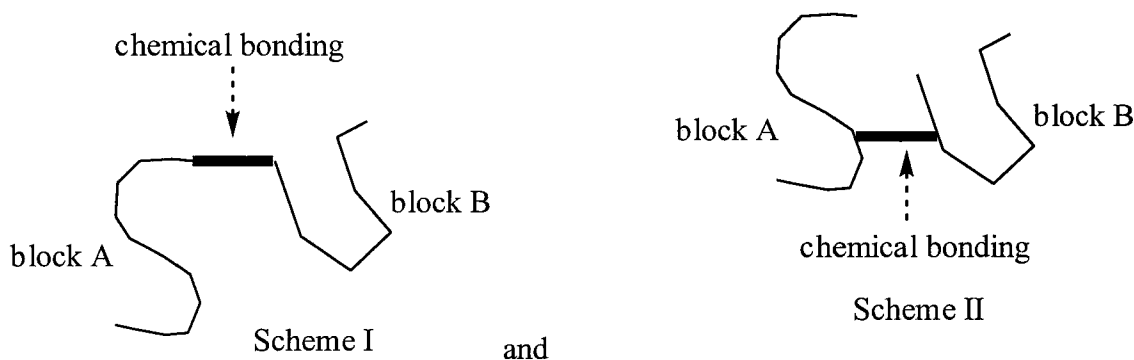
Claims 31-41, 47-49, 51 and 52 are rejected as being obvious over U.S. Patent No. 6,110,483 to Whitbourne et al. ("Whitbourne") in view of WO 2004/101018 ("WO101018").

Claim 31 defines a medical article comprising an implantable medical device and a coating deposited on at least a part of the device. The coating includes (a) a structural component comprising a linear acrylic homopolymer or linear acrylic copolymer; and (b) a biobeneficial component **comprising a copolymer having an acrylate moiety and a biobeneficial moiety.**

Whitbourne describes a coating formed of poly(butyl methacrylate) (PBMA). As the Examiner correctly notes, Whitbourne fails to describe or teach a coating that includes a biobeneficial component **comprising a copolymer having an acrylate moiety and a biobeneficial moiety.**

With respect to WO 101018, the Examiner alleges that the definition of block copolymer by Applicant would cause the physical mixture of homopolymers of PEG and PMBA as

disclosed in WO 101018 to qualify as a block copolymer because Applicant defines a block copolymer as one that “needs not be linked at ends.” Applicant respectfully submits that the Examiner’s assertion is unfounded. By definition, a block copolymer is a polymer that includes at least two chemically bonded blocks. The chemical bonding between the two blocks can occur at the ends of the two blocks or at the side of the two blocks, e.g., bonding via a pendant group in the blocks. To be clear, the two situations are illustrated in the schemes below:



Scheme I illustrates a block copolymer having two blocks where the two blocks are chemically bonded at the ends of the two blocks. Scheme II illustrates a block copolymer having two blocks where the two blocks are chemically bonded at the sides, but not the ends, of the chains of the two blocks. **Applicant’s definition of the block copolymer encompasses block copolymers as Schemes I and II illustrate but not a physical mixture of two homopolymers to a person of ordinary skill in the art of polymer chemistry.**

In sum, WO 101018 fails to make up the deficiencies of Whitbourne with respect to the medical article as defined by claim 31. Claim 31 is patentably allowable over Whitbourne under 35 U.S.C. §103(a). Claims 32-41, 47-49, 51 and 52 depend from claim 31 and are patentably allowable over Whitbourne under 35 U.S.C. §103(a) for at least the same reason.

The undersigned authorizes the examiner to charge any fees that may be required or credit of any overpayment to be made to Deposit Account No. 07-1850.

CONCLUSION

Withdrawal of the rejection and allowance of the claims are respectfully requested. **If the Examiner has any suggestions or amendments to the claims to place the claims in condition for allowance, applicant would prefer a telephone call to the undersigned attorney for approval of an Examiner's amendment.** If the Examiner has any questions or concerns, the Examiner is invited to telephone the undersigned attorney at (415) 393-9885.

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Respectfully submitted,

/ZLI/
Zhaoyang Li, Ph.D., Esq.
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Electronic Acknowledgement Receipt

EFS ID:	3095464
Application Number:	10815421
International Application Number:	
Confirmation Number:	7688
Title of Invention:	Biocompatible polyacrylate compositions for medical applications
First Named Inventor/Applicant Name:	Syed F.A. Hossainy
Correspondence Address:	Cameron K. Kerrigan Squire, Sanders & Dempsey L.L.P. Suite 300 1 Maritime Plaza San Francisco CA 94111 US 4159540200 -
Filer:	Zhaoyang Li/LaRenda Meyer
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Filing Date:	31-MAR-2004
Time Stamp:	13:49:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment After Final	359.pdf	679485	no	22
			eca0d91cadfcd8ed722805f3df750a8f4aabe9c8		

Warnings:

Information:

Total Files Size (in bytes):	679485
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875					Application or Docket Number 10/815,421		Filing Date 03/31/2004		<input type="checkbox"/> To be Mailed	
APPLICATION AS FILED – PART I										
(Column 1)			(Column 2)		SMALL ENTITY <input type="checkbox"/> OR		OTHER THAN SMALL ENTITY			
FOR	NUMBER FILED	NUMBER EXTRA	RATE (\$)	FEE (\$)	OR	RATE (\$)	FEE (\$)			
<input checked="" type="checkbox"/> BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	770			
<input type="checkbox"/> SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A				
<input type="checkbox"/> EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A				
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X \$	=		X \$	=			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X \$	=		X \$	=			
<input type="checkbox"/> APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).									
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))										
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	770			
APPLICATION AS AMENDED – PART II										
(Column 1)			(Column 2)		(Column 3)		SMALL ENTITY OR		OTHER THAN SMALL ENTITY	
AMENDMENT	04/03/2008	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	OR	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	* 82	Minus	** 82	= 0	X \$	=		X \$50=	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X \$	=		X \$210=	0
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))									
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE			OR	TOTAL ADD'L FEE
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)	ADDITIONAL FEE (\$)	OR	RATE (\$)	ADDITIONAL FEE (\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X \$	=		X \$	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X \$	=		X \$	=
	<input type="checkbox"/> Application Size Fee (37 CFR 1.16(s))									
	<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE			OR	TOTAL ADD'L FEE
<p>* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.</p> <p>** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".</p> <p>*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".</p> <p>The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.</p>										

Legal Instrument Examiner:
/GLORIA TRAMMELL/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/815,421	03/31/2004	Syed F.A. Hossainy	50623.359	7688

7590 04/14/2008
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EXAMINER

SILVERMAN, ERIC E

ART UNIT	PAPER NUMBER
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1618

MAIL DATE	DELIVERY MODE
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04/14/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<p align="center">Advisory Action Before the Filing of an Appeal Brief</p>	<p>Application No. 10/815,421</p>	<p>Applicant(s) HOSSAINY, SYED F.A.</p>	
	<p>Examiner Eric E. Silverman, PhD</p>	<p>Art Unit 1618</p>	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 April 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: _____.
Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☒ Other: See Continuation Sheet.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Continuation of 11. does NOT place the application in condition for allowance because: Applicants aver that the office is incorrect in relying on the definition of block copolymer in the specification. Specifically, Applicant notes that the definition of block copolymer in the art is a polymer having two or more blocks of different monomers. While that is the standard definition in the art, it is recognized that Applicants may be their own lexicographers, and when Applicant clearly redefines a term in the specification so as to put the artisan on notice of the meaning that Applicant applies to the term, it is Applicants definition that governs. Here, the specification clearly redefines the term block copolymer to include situations where the two blocks are not linked at the end, which, when interpreted broadly but reasonably, includes situations where the blocks are not chemically bound to one another. The prosecution history has been quite clear as to the meaning attached to Applicants definition. Further, Applicant has had ample opportunity to amend the claims to require that the ends of the block copolymer be linked, but has declined to do so. Applicants' arguments are therefore not persuasive.

Continuation of 13. Other: Regarding Applicants' comments about various information disclosure statements, Office records indicate that every information disclosure statement that was submitted in this Application has been returned to Applicant. Contrary to Applicants' allegations, Office records do not indicate that any submission was filed on 9/7/2005. Irrespective of Applicant's assumptions, only those references that are listed on an IDS and initialled by the Examiner as having been considered, pursuant to applicable sections of the CFR and MPEP, were actually considered. Applicants assumptions do not trump Office rules and policies. Additional references may be considered if listed on an IDS that is submitted to the Office in a timely fashion.